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The risk of dying: Predicting trauma mortality in urban Indian hospitals

THE RISK OF DYING

Predicting trauma mortality in urban Indian hospitals

Martin Gerdin

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THE RISK OF DYING

Predicting trauma mortality in urban Indian hospitals

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By

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abstract

Introduction With increased urbanisation and motorisation, trauma is emerging as one of the top threats to population health globally. Each year almost five million people die as a result of trauma, more than the total number of deaths from HIV/AIDS, tuberculosis, malaria, and maternal conditions combined. An overwhelming majority of these deaths occur in low- and middle-income countries, and almost 20% occur in India alone. In high income countries trauma mortality has been successfully reduced by extensive primary prevention and implementation of trauma systems. A systematic approach to prioritising patients according to needs is a crucial component of such systems. Several so called prediction models, i.e. often statistically derived algorithms to estimate the risk of mortality in an individual, have been developed to aid in this process. However, many available prediction models for trauma care have methodological limitations. Therefore, this research aimed to develop such a prediction model for an Indian trauma context.

Methods In study I [I] three cohorts of trauma patients admitted to a single centre in Mumbai were studied. Models were developed using multivariate logistic regression to assess the temporal trends in trauma mortality between 1998 and 2011. In study II [II] a prospective cohort study was conducted in three public university hospitals across urban India to derive vital signs based prediction models for early trauma mortality. Stepwise logistic regression was used to identify main effects. Then, in study III [III], the models derived in study II were validated temporally and compared with recently published prediction models. Validation was performed by applying the models in a temporally independent sample compared to study II. Finally, in study IV [IV] the transferability of vital signs-based prediction models was assessed by deriving models both in data from public university hospitals in India and data from the National Trauma Data Bank in the United States.

Main findings Analysis of 4189 trauma patients showed that early mortality significantly decreased between 1998 and 2011 [I]. Two models for predicting early mortality were derived using data from a prospective cohort of 1689 adult trauma patients admitted between October 2013 and January 2014. The first model included systolic blood pressure and Glasgow coma scale and the second model included systolic blood pressure, heart rate, and Glasgow coma scale [II]. These models were validated in a temporally independent sample of 2811 adult trauma patients. There was no evidence that comparatively more complex models had better predictive performance than the model with only systolic blood pressure and Glasgow coma scale [III]. Finally, when applied in data from another context, i.e. transferred, models from India overestimated the risk of early mortality in patients from the United States. In contrast, models from the United States underestimated the risk in patients from India. This miscalibration could be adjusted using updating methods in small samples [IV].

Conclusions Between October 2013 and July 2014 early mortality was about 8% in adult trauma patients presenting to three public university hospitals in urban India. Substantial differences in systolic blood pressure and Glasgow coma scale between non-survivors and survivors indicate that haemorrhage and traumatic brain injury are major clinical issues. In prioritising trauma patients Indian clinicians and policy makers should consider to including vital-sign based decision support. The model based on systolic blood pressure and Glasgow coma scale presented here may help in this process. Finally, future validation studies of logistic prediction studies should explicitly include an updating component.

populärvetenskaplig sammantfattning

Trauma är kroppsskada i kombination med kroppens svar på skada. Varje år dör nästan fem miljoner människor av trauma. Det är fler än det sammanlagda antalet människor som årligen dör av malaria, tuberkulos, HIV/AIDS och mödradödlighet. Nästan 90% av alla traumadödsfall sker i låg- och medelinkomstländer. Enligt modern forskning skulle två miljoner liv kunna räddas varje år om man lyckades sänka traumadödligheten i låg- och medelinkomstländer till samma nivå som i höginkomstländer som Sverige.

Indien är ett medelinkomstland. Varje år dör cirka en miljon människor av trauma i Indien. Det är en femtedel av hela världens traumadödsfall. Därför är det viktigt med forskning som syftar till att identifiera och utveckla åtgärder som kan minska traumadödligheten i Indien. I höginkomstländer har man lyckats reducera dödligheten från trauma genom att satsa på förebyggande åtgärder. Man har också utvecklat system för att identifiera de mest kritiskt skadade patienterna och prioritera dessa. Som en del av sådana system används modeller för att förutsäga risken för död bland traumapatienter. En patient med högre risk att dö anses då som mer kritiskt skadad än någon med lägre risk.

En sådan modell skulle potentiellt kunna användas i Indiska sjukhus för att bedöma vilka patienter som behöver omedelbar vård. Tyvärr har de flesta modeller som används för att förutsäga risken för död utvecklats i höginkomstländer. Många av dessa modeller innehåller parametrar som sällan mäts på Indiska sjukhus vilket gör dem svåra att använda. De innehåller också parametrar som är svåra att uppskatta om patienten är medvetlös, till exempel ålder och skademekanism. Därför syftar denna avhandling till att utveckla en modell för att förutsäga risken för död bland vuxna traumapatienter som kommer till Indiska sjukhus.

Forskningen bedrevs huvudsakligen på tre offentliga universitetssjukhus i städerna Mumbai, Delhi och Kolkata. Fyra studier har genomförts. Den första studien syftade till att granska hur dödlighet inom 24 timmar efter ankomst till sjukhus bland traumapatienter har förändrats mellan 1998 och 2011. Den visade att dödligheten minskade bland patienter med allvarligt trauma. Studie två och tre syftade till att utveckla en modell för att förutsäga risken att dö bland vuxna traumapatienter. Dessa studier visade att systoliskt blodtryck och medvetandegrad mätt enligt skalan Glasgow coma scale kunde förutsäga risken att dö med gott resultat. Den fjärde studien syftade till att bedöma om man kan använda en modell utvecklad med Indiska data i USA och tvärtom. Denna studie visade att den Indiska modellen överskattade risken att dö i USA och att den amerikanska modellen underskattar risken att dö i Indien.

Dessa resultat tyder på att:

- **Risken** för att dö bland traumapatienter som kommer till sjukhusen som deltog i denna forskning kan förutsägas genom att man mäter systoliskt blodtryck och medvetandegrad.
- **Modellen** innehåller bara två parametrar vilket är färre än de modeller som idag används i många höginkomstländer. Den kräver dessutom ingen huvudräkning vilket borde göra den enklare att applicera än många befintliga modeller.
- **Om** man som vårdgivare eller vårdpersonal vill använda sig av en modell som utvecklats någon annanstans måste man vara medveten om risken att den antingen överskattar eller underskattar. Detta kan dock åtgärdas med statistiska uppdateringsmetoder.

“ *there are no accidents*”
- Master Oogway

From the movie Kung Fu Panda (2008)

ac·ci·dent

: a sudden event (such as a crash) that is not planned or intended and that causes damage or injury

: an event that is not planned or intended

: an event that occurs by chance

Definition from www.merriam-webster.com

preface

I'm the kind of person who likes springs and autumns the most. To me, they are beginnings. Different kind of beginnings. But beginnings nevertheless. I dread the in-betweens. I fear the void. I hate endings. I don't know why, but I grow restless easily. My feet start tapping. I walk in circles. I prefer the unpredictability of something new. Because it keeps me occupied. And I need to be occupied because if I'm not occupied, then what am I? If I'm given too much time then... I. Get. Nothing. Done. Lately, Johan has often asked me why I decided to do this the way I did. I guess the answer is that I don't know any other way. And now it's done.

You want to know the beginning of all this? Well, there was not one beginning but many. It began with Haiti. It began when the earth came alive and brought death. It began with an email to Johan when he got back from the rubble. Back then, my thesis was supposed to be on the foreign medical teams that went to Haiti. That didn't work out because of difficulties with collaborators and a deteriorating security situation in Haiti. The research got me to a disaster medicine congress in Beijing though. In Beijing our group was to arrange a seminar on the response to Haiti. A sudden cancellation left a slot empty. No one agreed to jump in on such short notice. Except Nobhojit, the Indian. He has always much to say.

Nobhojit later stopped by Sweden on his way somewhere else. I was a useless local guide. But in a taxi between two hospitals we agreed that I should come to Mumbai to learn surgery. And so I did. Because traumatology and critical care was and is my primary clinical interest I spent a lot of time in the trauma operating room and the trauma intensive care unit. As a student I was expected to observe. I observed the staff's tireless efforts to save the patients wheeled into the casualty. I observed the strength it took to wake up and focus on yet another trauma case after finally catching some rest after working hours after hours in a row with no sleep.

At the same time, I also noticed a lack of structure and systematic approach to trauma management. I became aware of how rarely nurses participated in actual clinical care. Being fostered in the Swedish health system I was firmly convinced that protocols, guidelines, and extensive documentation, i.e. systems, are the solution to all health care challenges. The research questions of this thesis emerged as attempts to provide one of building blocks of such systems, namely the basis for decision support.

I don't think master Oogway meant that there are no accidents. There are simply too many accidents. I think what he meant was that everything can be predicted. That prediction is everything. Because we all do it all the time. Every – if – then – what – is a prediction. I believe that most accidents can be predicted. And if they can be predicted they can be avoided. Death is not an accident. In fact, it may be the only thing in life that we can be sure of. But accidents cause death. In India accidents cause an awful lot of death all the time. I think that like accidents death can be predicted. Not avoided, but delayed. If we predict. An end becomes a beginning. Therefore, the risk of dying has kept me occupied.

list of scientific papers

- I.** Gerdin M, Roy N, Dharap S, Kumar V, Khajanchi M, Tomson G, Felländer-Tsai L, Petzold M, von Schreeb J. (2014) Early Hospital Mortality among Adult Trauma Patients Significantly Declined between 1998-2011: Three Single-Centre Cohorts from Mumbai, India. *PLoS ONE* 9(3): e90064. doi: 10.1371/journal.pone.0090064
- II.** Gerdin M, Roy N, Khajanchi M, Kumar V, Dharap S, Felländer-Tsai L, Petzold M, von Schreeb J. (2014) Predicting Early Mortality in Adult Trauma Patients Admitted to Three Public University Hospitals in Urban India: A Prospective Multicentre Cohort Study. *PLoS ONE* 9(9): e105606. doi: 10.1371/journal.pone.0105606
- III.** Gerdin M, Roy N, Khajanchi M, Kumar V, Felländer-Tsai L, Petzold M, Tomson G, von Schreeb J. Simplifying complexity: A validation study of prediction models for early mortality in adult trauma patients in three public university hospitals in urban India (submitted)
- IV.** Gerdin M, Roy N, Felländer-Tsai L, Tomson G, von Schreeb J, Petzold M. Traumatic transfers: Calibration is adversely affected when prediction models are transferred between trauma care contexts in India and the US (submitted)

The papers are henceforth referred to using their roman numerals I-IV

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list of abbreviations

ACS	American College of Surgeons
AIIMS	All India Institute for Medical Sciences
AUROC	Area Under the Receiver Operating Characteristics Curve
CARS	Compensatory Anti-inflammatory Response Syndrome
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CT	Computed Tomography
CONSORT	Consolidated Standards of Reporting Trials
DALYs	Disability Adjusted Life Years
DAMP	Damage-Associated Molecular Patterns
HIV/AIDS	Human Immunodeficiency Virus Infection and Acquired Immune Deficiency Syndrome
ICD	International Classification of Disease
ICISS	International Classification of Disease Injury Severity Score
IQR	Inter-Quartile Range
ISS	Injury Severity Score
JPNATC	Jai Prakash Narayan Apex Trauma Center
LTMGH	Lokmanya Tilak Municipal General Hospital
MDGs	Millennium Development Goals
MeSH	Medical Subject Headings
MODS	Multiple Organ Dysfunction Syndrome
NCD	Non-Communicable Disease
NLM	National Library of Medicine
NTDB	National Trauma Data Bank
OR	Odds Ratio
SDGs	Sustainable Development Goals

SIRS	Systemic Inflammatory Response Syndrome
SRR	Survival Risk Ratio
SSKM	Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital
TITCO	Towards Improved Trauma Care Outcomes
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
UHC	Universal Health Coverage
UN	United Nations
USA	United States of America
WHO	World Health Organization

definitions

Complex adaptive system	A collection of individual agents that have the freedom to act in ways that are not always predictable and whose actions are interconnected such that one agent's actions changes the context for other agents (1).
Early mortality	Death in hospital during the first 24 hours after admission, arrival, or time when the first set of vital signs was recorded (2, 3).
Free parameter	A numerical factor included in a statistical model, excluding the model intercept. A variable may be transformed so that its association with the outcome of interest is represented by several free parameters.
Health system	All organizations, people and actions whose primary intent is to promote, restore or maintain health (4).
Injury	Damage inflicted on the body as the direct or indirect result of an external force, with or without disruption of structural continuity (5).
Prediction model	An algorithm, often derived using statistical methods, based on two or more predictors that may be used to estimate the risk of a specific outcome in an individual (6).
Prediction model derivation	The generation of a prediction model, i.e. the selection of main effects (6, 7).
Prediction model development	The process of deriving and validation a prediction model (6, 7).
Prediction model validation	The evaluation of a prediction model. This can be done in the same dataset as used for derivation, and then be called internal validation, or in a different dataset, called external validation (6, 7).
Predictor	A prognostic factor that can be used to estimate a probability of the outcome of interest in future individuals.
Prognosis	The expected course of illness in a particular individual (8).
Prognostic factor	Any factor that in people with a specific health condition is associated with the outcome of interest (9).
Risk factor	A prognostic factor that is associated with an increased probability of the outcome of interest.
Systems thinking	An enterprise aimed at seeing how things are connected to each other within some notion of a whole entity (10).
Trauma	The clinical entity composed of physical injury and the body's associated response.
Variable	A clinical factor of interest, for example systolic blood pressure.

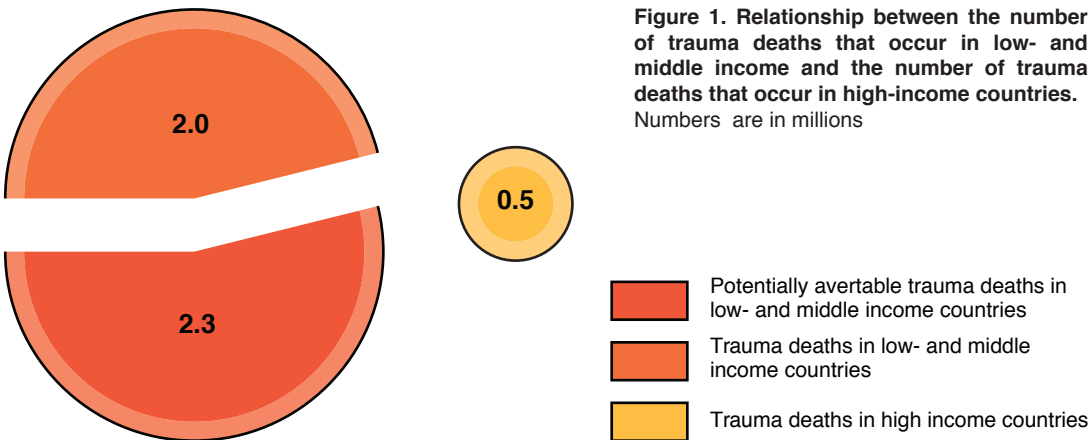
introduction

Humanity is now looking to expand reality by populating other worlds (11). Some view this as a prerequisite for the survival of human race (12). According to the think tank Global Footprint Network what is called the “Earth Overshoot Day”, i.e. the day when the world’s annual ecological resources are spent, is happening increasingly early (13). This depletion of biocapacity is closely associated with global population size. When this sentence was written the world was home to 7,292,211,232 people (14). Some scientists argue that the most likely scenario is that the world’s population will peak at about nine billion people in 2070 and then slowly decline (15, 16). Others believe that it is highly unlikely that the world’s population will stabilize anytime this century (17).

A growing global population causes substantial challenges to human health. Still, major improvements have been achieved worldwide during the last 25 years in terms of human development. Compared to 1990 the proportion of people living in extreme poverty, i.e. less than \$1.25 per day, has been reduced from 47 to 14%. During the same time period the number of children of primary school age that did not attend school almost halved, the number of deaths in children aged less than five years declined by 6.7 million, and maternal mortality dropped by 45%. Furthermore, substantial successes have been achieved in combating HIV/AIDS, malaria, and tuberculosis (18), diseases that up till recently were accountable for the brunt of global burden of disease (19).

These achievements were part of the United Nations (UN) Millennium Development Goals (MDGs) (18). Although some of them have been reached significant challenges remain. Many of these persistent challenges are associated with an ongoing epidemiological transition. Today, trauma (Panel 1) and non-communicable diseases (NCDs) such as ischemic heart disease, cerebrovascular disease, and diabetes, have surpassed communicable diseases both in terms of mortality and morbidity (19). To combat these challenges, and to follow up on the MDGs, the UN is now in the process of defining so called Sustainable Development Goals (SDGs) (20). These goals include the eradication of poverty and ensuring healthy lives for all.

To ensure healthy lives for all the UN has vowed to reduce global trauma mortality by halving the number of deaths that result from road traffic accidents by 2020. This reduction is part of SDG 3 and as a commitment it reflects a growing international understanding of trauma as a public health threat. Every year more than five million people die because of trauma (19). This



is more than the total number of deaths from malaria, tuberculosis, HIV/AIDS, and maternal conditions combined. Over 90% of trauma deaths occur in low- and middle income countries (Table 1) (21). If the trauma death rates in low- and middle income countries were reduced to the same levels as in high income countries almost two million lives could be saved each year (Figure 1) (22).

India accounts for close to 20% of global trauma mortality (23). Reducing mortality in this one of the world's trauma hotspots should therefore be a global priority. However, how to best achieve this reduction constitutes a significant knowledge gap. In high income countries efforts have focused on strengthening the trauma system, defined as a continuum of interventions ranging from primary prevention to rehabilitation (24). Although primary prevention such as improving road safety is key to reducing trauma mortality high quality care will always be needed to manage trauma victims.

Table 1. Selected indicators by World Bank country income group

	Low income	Lower middle income	Upper middle income	High income
Examples of countries in this group	Afghanistan, Cambodia, Nepal, Zimbabwe	Bolivia, India, Nigeria, Ukraine	Algeria, Colombia, Maldives, Turkey	Argentina, Denmark, Italy, Singapore
GNI cutoff (\$)*	≤1,035	1,036-4,125	4,126-12,735	≥12,736
Total population (in millions)	622	2,879	2,361	1,399
GNI per capita (\$)*	626	2,012	7,873	38,317
Life expectancy at birth (years)	62	66	74	79
Population living in urban areas (%)	30	39	62	81
Total fertility rate (births per woman)	4.8	2.8	1.9	1.7
Maternal mortality ratio (per 100,000 live births)	510	240	57	22
Under 5 mortality rate (per 1,000 live births)	76	53	19	7
Vehicles (thousands)	10,047	295,800	444,700	803,400
Vehicle density (per 100,000 population)	1,615	10,274	18,836	57,429
Road traffic deaths (per 100,000 population)	21.1	18.3	17.7	9.8

Data from the World Bank Open Data and the World Health Organization Global Health Observatory Data (65, 66). No data is from earlier than 2010. *The World Bank's country classifications are based on the per capita GNI for the previous year. GNI is calculated using the World Bank Atlas method. Abbreviations: GNI Gross National Income

One crucial component of a trauma system is a structured approach to the initial trauma patient management. Many decision support tools have been developed to aid this process. These tools often build on so called prediction models. In this thesis a prediction model is defined as an algorithm, often derived using statistical methods, based on two or more predictors that may be used to estimate the risk of a specific outcome in an individual (6). Most prediction models for trauma care use mortality as the outcome. However, many available prediction models for trauma care include parameters that are not routinely measured in Indian trauma contexts, or parameters that are not always available on initial examination. Furthermore, many published prediction models have methodological limitations (25). Therefore, this thesis is about developing such a prediction model for an Indian context.

Panel 1. Definitions of trauma and injury

This panel is an attempt to clarify the difference between trauma and injury. In the international literature these concepts are often used interchangeably. Even hybrids such as "traumatic injury" are used. For example, the journal named *Injury* deals with "all aspects of trauma care and accident surgery" (26). A search using the string "trauma" in the U.S. National Library of Medicine (NLM) Medical Subject Headings (MeSH) browser returns the MeSH heading "Wounds and Injuries". If you search for "injury", you end up in the same place. According to NLM "[Wounds and injuries are] damage inflicted on the body as the direct or indirect result of an external force, with or without disruption of structural continuity" (5).

Injury can be classified using different systems such as the International Classification of Disease (ICD) (27). For example, a fracture of the shaft of femur would be coded as S72.30 if it is closed, S72.31 if it is open. Injury is the preferred term in the public health literature, especially in terms of injury prevention. The actual physical injury is however only the beginning of a whole range of interlinked bodily responses (Panel 2) (28). For example, an open femoral shaft fracture with soft tissue and vascular injury is associated with significant bleeding. Haemorrhage activates the coagulation cascade, causes a systemic inflammatory response, and left untreated leads to haemodynamic instability and potentially death.

These responses are caused by injury, but not part of the injury, and often require active treatment in addition to treatment of the original injury. Traumatology can be defined as "the medical speciality which deals with wounds and injuries as well as resulting disabilities and disorders from physical traumas" (29). Hence, I define trauma as the clinical entity composed of the combination of physical injury and the body's associated responses. Throughout this thesis the term injury will be used to denote the actual physical injury whereas trauma will be used to refer to this clinical entity.

state of the art

Systems thinking and context

Developing a prediction model for an Indian trauma care context involves applying mechanical systems thinking when dealing with a complex adaptive system. Systems thinking is “an enterprise aimed at seeing how things are connected to each other within some notion of a whole entity” (10). In mechanical systems there is a linear relationship between input and output. Unless there is an error it does not matter where you place the machine, as long as the input is the same it will still produce the same output. In other words, a machine is not context sensitive (1). This type of systems thinking is relevant to this thesis because the development of a prediction model involves a fair amount of machine systems thinking. This will be elaborated on later.

The opposite of mechanical systems thinking is complex adaptive systems thinking. A complex adaptive system has been defined as “a collection of individual agents that have the freedom to act in ways that are not always predictable and whose actions are interconnected such that one agent’s actions changes the context for other agents” (1). In other words, the relationship between input and output is highly non-linear. The World Health Organization (WHO) has defined a health system as consisting of “all organizations, people and actions whose primary intent is to promote, restore or maintain health” (4). In essence, health systems are thought of as composed of six components, or building blocks (Figure 2) (4, 30):

- Service delivery
- Human resources
- Information
- Medical products, vaccines and technologies
- Financing
- Governance

Health systems are complex adaptive systems because of the intricate ways these different components interact. For example, why do different parts of the world need different models for how get trauma patients to hospital (31)? Why do we use ambulances in some parts and taxi-drivers in others? According to mechanical systems thinking a model that works in one part of the world should work equally well in another part of the world.

The answer is context. In contrast to mechanical systems complex adaptive systems are context sensitive. Different parts of the world differ in terms of income-, age-, and sex distribution as well as culture, political systems, climate and so forth. In some places ambulances are neither affordable nor feasible due to low availability of resources to this end and traffic so heavy that ambulances would reach far too late anyway. In the medical literature today the World Bank’s income-based country groups are often used to describe context (Table 1) (32). Although this classification is useful to depict context in the broad sense it hides large variations within groups and within countries.

Within the subject area critical care Tim Baker recently defined the concept “low resource setting” as a context “with few material and financial means” (33). In his work, Baker highlighted that this concept is not synonymous with low income country. Similarly in this thesis a low resource trauma context is defined as characterised by substantial limitations in resource availability, within all health systems building block. In such a context facilities catering to

trauma patients are few and systems to facilitate patients reaching care are inadequate. Health care providers are rarely trained in trauma care and education programs are largely missing. There are lacunas in available medicines and equipment and out-of-pocket payments to finance the care is prevalent. Policies and legislation to prevent trauma is poorly enforced.

Subsequently, a high resource trauma context is the opposite of a low resource trauma context. All the world's different trauma contexts can then be conceptually arranged on a spectrum ranging from low- to high resource. Importantly, and as in critical care, low resource trauma contexts do not only exist in low income countries and high resource trauma contexts do not only exist in high income countries, although a correlation between country income group and the prevalence of different trauma contexts definitely exists. That said, multiple different trauma care contexts may exist within a single country and even within a single state or region.

Trauma systems are embedded into health systems

Health systems globally are faced with severe challenges. Human life and activity is today increasingly characterised by international connectivity and mobility. People, information, services, technology, capital, and microbes now travel more or less freely across national and international borders. Local practices are marketed globally and global trends are adapted to local contexts through processes of globalisation and glocalisation (34). The rates at which all this is happening are unprecedented and health systems need to adapt. A concrete example of how these processes currently outrun health systems is the aggressive marketing of alcohol in relatively naïve contexts (35).

During recent years the global understanding of the importance of health systems in promoting and maintaining population health has increased. Central to achieving healthy lives for all is the concept of universal health coverage (UHC), defined as high-quality health care for all at an affordable cost (36). This is demonstrated by the fact that the UN “pledge to strengthen health systems towards the provision of equitable universal coverage” (37). The need to strengthen health systems, primarily in low- and middle income countries, was one of the key messages of the Lancet Commission on Global Health 2035 (38). In their report, Jamison and Summers et al. highlight that strong health systems are a prerequisite if the increasing burden of trauma and NCDs is to be halted (Table 2).

The trauma system can be conceptualised as embedded within the health system. The concept originated in the US (39), and today it encompasses prevention, prehospital and hospital care, as well as rehabilitation (24). A substantial body of research indicates that the implementation of trauma systems has improved patient outcomes primarily in high resource trauma contexts (40-44). However, trauma systems globally, and trauma systems in low- and middle income countries in particular, do face challenges within all six building blocks (Table 3).

Health systems in India

India is the world's second most populated country with close to 1.3 billion inhabitants (Figure 3 and Table 4) (45). In the 2014 general elections over 66% of the more than 830 million eligible voters participated, making India the largest democracy in the world (46). It is a highly diverse country in terms of culture and religion, with Hinduism and Islam being the two dominating religions. Today, about 35% of India's population lives in urban areas. Several

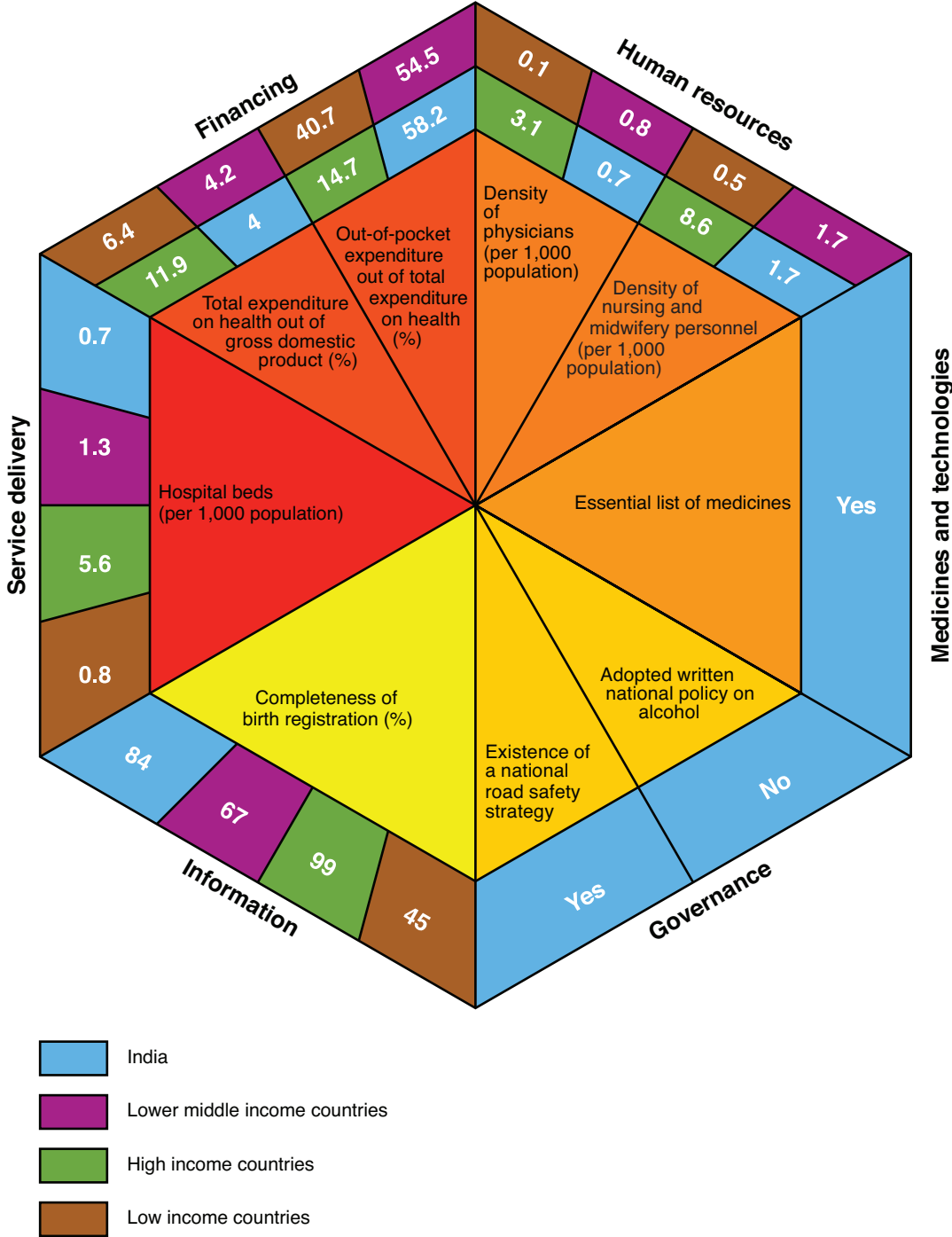


Figure 2. Schematic overview of the six health system building blocks. Examples of indicators. Data from The 2014 update, Global Health Workforce Statistics, World Health Organization, Geneva and the World Bank

Table 2. Examples of health systems constraints across six levels from the community to the global level and how these constraints may be interpreted from a trauma perspective

Level	Example of constraint	Applied to trauma
Community and household	Barriers to use of effective interventions (physical, financial, social)	Long distances to closest health facility equipped to manage trauma patients
Service delivery	Shortage and poor distribution of appropriately qualified staff	Shortage of health care providers trained in trauma patient management
	Lack of equipment and infrastructure	Lack of equipment to secure and manage a threatened airway
Policy and strategic management in the health sector	Weak drug policies and supply systems	Poor supply systems to ensure rapid blood transfusion
Government policy	Limited communication and transport infrastructure	Difficult to ensure transfer routes for trauma patients
Political and physical environment	Governance and overall policy framework (e.g. corruption, weak government, weak rule of law and enforceability of contracts etc.)	Barriers to establish and implement national coordination of trauma services and research
Global	Fragmented governance and management structures for global health	Poor funding opportunities for trauma research
	Emigration of doctors and nurses to high income countries	Drain of health care providers skilled in trauma patient management

Data from the World Bank Open Data and the World Health Organization Global Health Observatory Data (65, 66). No data is from earlier than 2010. *The World Bank's country classifications are based on the per capita GNI for the previous year. GNI is calculated using the World Bank Atlas method. Abbreviations: GNI Gross National Income

of the world's largest cities are located in India, both Delhi and Mumbai have more than 20 million residents whereas about ten million people live in each of Kolkata, Bengaluru, and Chennai (45). In 15 years an additional 250 million people are projected to have shifted into urban settlements (47).

The country has made remarkable economic progress during recent years and by 2050 India together with China and Brazil are projected to account for 40% of the global economic output (48). India and China has been named as the “fastest growing major economies in the world”. So far in 2015 the annual economic growth has been about 7% (49). This is slightly lower than the 8-8.5% growth experience annually between 2004 and 2009, which in turn was substantially higher than between 1993 and 2004 when growth was about 6%. Although all states in India have experienced economic growth, poverty inequality has increased as income differences between states grew and consumption power has increased more in urban compared to rural areas (50).

Despite the substantial threats posed to India's health systems by the unprecedented rate of urbanisation, growing inequality, and the ongoing epidemiological transition the country has made considerable progress in terms of reducing both child and adult mortality during recent years (19). The central government, represented by the Union Ministry of Health and Family Welfare, is responsible for national coordination, national policies, assist local health authorities, and funding for national health initiatives. The corresponding body on state level, the State

Department of Health and Family Welfare, is responsible for service delivery within each state (51).

India's health system has been criticised for being highly inequitable (52), and health expenditures have been reported as one of major factors that cause Indian households to fall below the poverty line (53). Public spending on health care is only 1% of the gross domestic product (GDP) and out-of-pocket payments make up almost 59% of the national health expenditure (54). India has a major private health sector and according to official figures the private sector accounts for 80% of doctors and 60% of inpatient care (54). Governmental initiatives to improve population health and achieve UHC have increased during recent years (55, 56).

Trauma systems in India

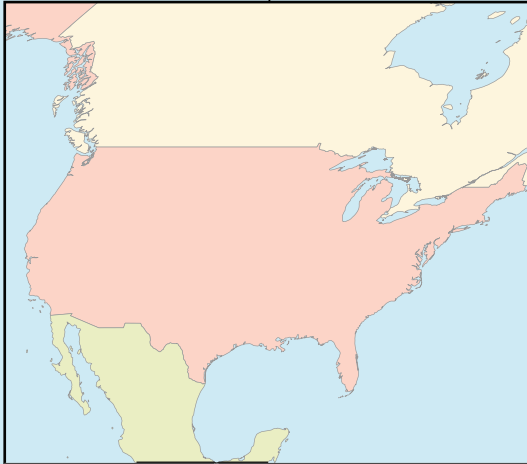
Trauma is often referred to as one of the top threats to population health in India (57, 58). Urbanisation and increased motorisation are quoted as key reasons. Although the publications on trauma systems in India are largely of the anecdotal sort, the country seems to lack an

Table 3. Examples of challenges and opportunities for trauma systems in low- and middle income countries

Health system building block	Examples of building block components	Challenges and opportunities
Human resources	Health care providers dedicated to trauma care	Health care providers involved in trauma care as part of treating patients in the emergency department are rarely trained in trauma care (89-92).
Medicines and technologies	Rapid availability of blood components and equipment for airway management	A recent review indicated that only about half of 531 hospitals across 17 countries have a functioning blood bank, or the equipment necessary to establish a secure airway (93). Limited skills and equipment necessary to establish a secure airway may reflect the fact that there are no means to care for patients once they are for example intubated as there are no or few ventilators (92).
Governance	Systems for trauma team oversight, audit, and education	Oversight committees as well as guidelines and systems for audit or education are rarely instituted outside mature trauma systems (89, 91, 94).
Information	Electronic medical records	Electronic medical records are poor or not implemented (90, 92).
	Trauma registries	The global distribution of trauma registries has been found to be heavily skewed towards high-income countries (95). Trauma registries are feasible in more resource-constrained contexts (96), even in the absence of complete electronic medical records (82).
Service delivery	A team approach to the management of trauma patients	Trauma team training has been showed to significantly improve knowledge on trauma management (97).
Financing	Include trauma care as part of universal health coverage initiatives	Trauma is associated with a significant risk of catastrophic health expenditures* (98).

*Defined as >30% of annual household income

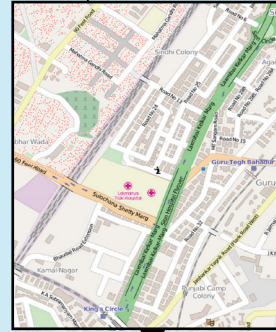
Study IV



UNITED STATES OF AMERICA

Land area (sq km)	9,161,966
Population	321,368,864
Population growth rate (%)	0.78
Median age (years)	37.6
Births (/1,000 population)	12.49
Deaths (/1,000 population)	8.15
Sex ratio male/female	0.97

Study I

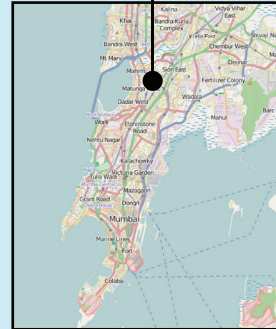


LTMGH

Beds
1,4000

**Admission
(/year)**
60,000

Dedicated trauma
14

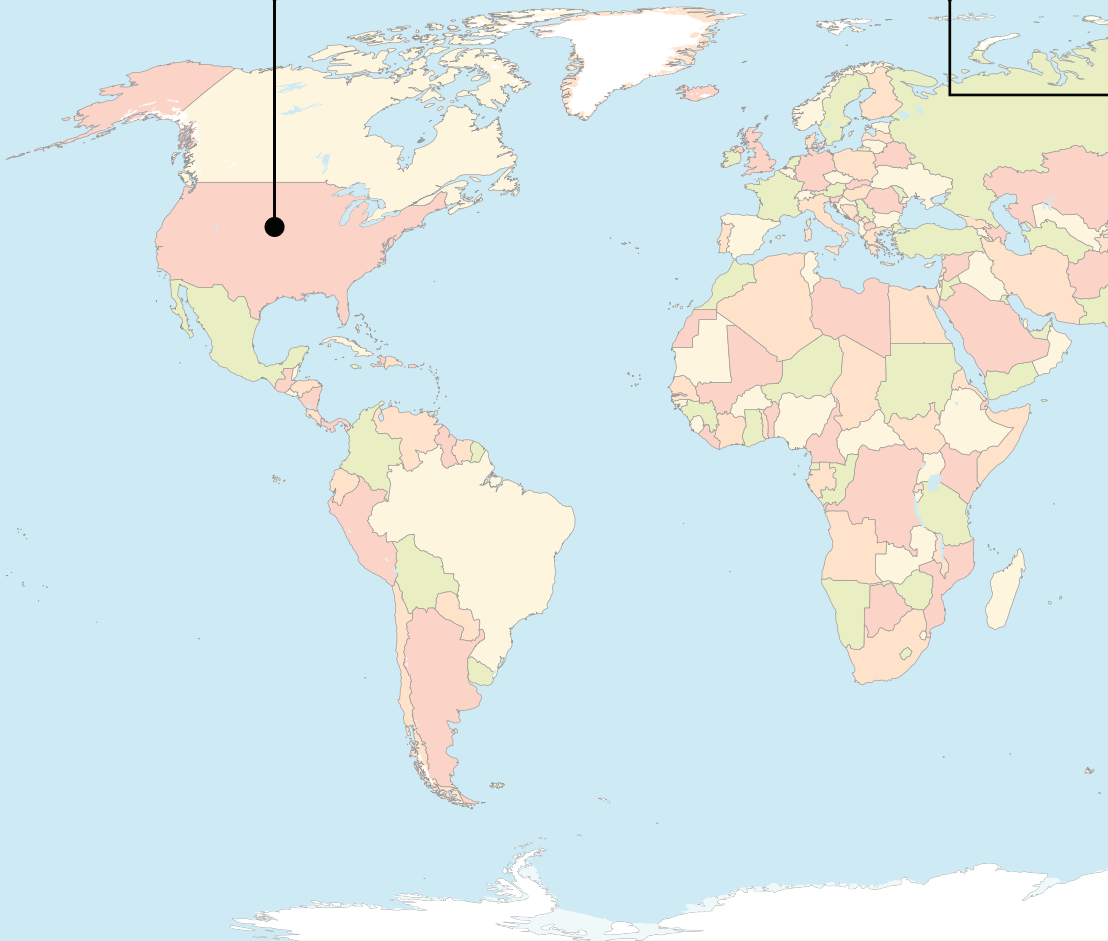


Mumbai

Population
21,043,000

**Population density
(/sq km)**
29,650

**Hospital beds
(/1000 population)**
2.55

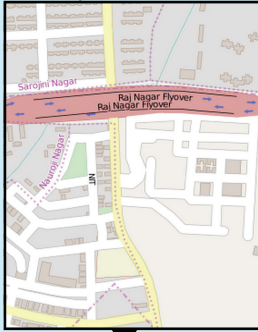


Study II and III

uma beds

nsity

ion)



JPNATC

Beds

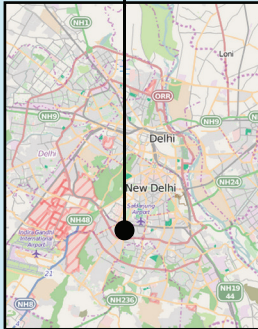
180

Admission (/year)

5400

Dedicated trauma beds

180



New Delhi

Population

25,703,000

Population density (sq km)

11,320

Hospital beds (/1000 population)

2.17



SSKM

Beds

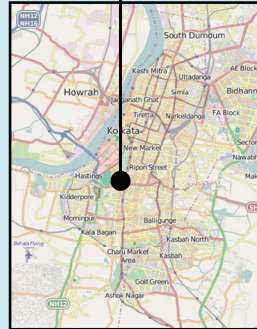
1500

Admission (/year)

30,500

Dedicated trauma beds

0



Kolkata

Population

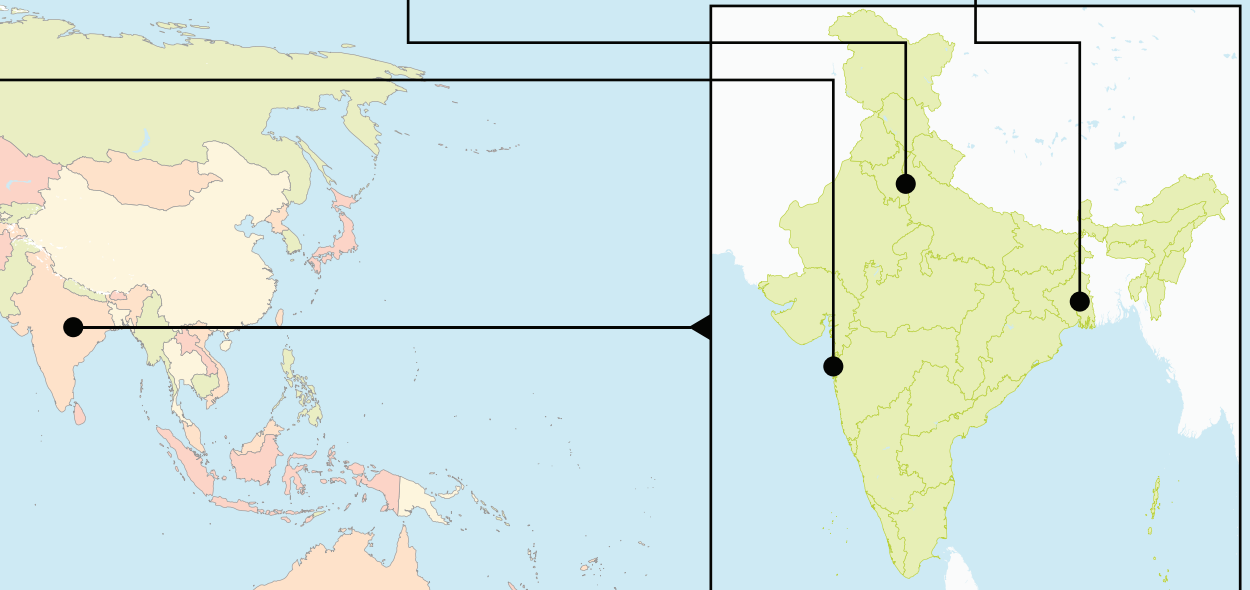
11,766,000

Population density (sq km)

24,306

Hospital beds (/1000 population)

6.17



REPUBLIC OF INDIA

Land area (sq km)	2,973,193
Population	1,251,695,584
Population growth rate (%)	1.22
Median age (years)	27
Births (/1,000 population)	19.55
Deaths (/1,000 population)	7.32
Sex ratio male/female	1.08

Figure 3. Outline of the study areas. Data from the Central Intelligence Agency's The World Factbook, India's city census 2011, Department of Health & Family Welfare, Government of West Bengal, SSKM Annual Report for the Year 2013, JPNATC Emergency Department Admissions Census 2010, The economic times, Bombay First, LTMGH website. Abbreviations: Jai Prakash Narayan Apex Trauma Center, LTMGH Lokmanya Tilak Municipal General Hospital, SSKM Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital. City maps © 2015 Google.

organised trauma system. In terms of governance policies and legislation intended to prevent trauma, such as laws on helmet and seat belt use, are poorly enforced (59). Legislation and policies to ensure high quality trauma care, such as accreditation of hospitals, are lacking (57). Regarding financing there have been successful attempts to include trauma care in India's efforts toward UHC (60), even though the health system in general and hence the trauma system is regarded as under funded (57, 59).

There is a substantial shortage of human resources dedicated to trauma care. Health care providers trained in trauma care are rare and often it is the most junior physicians who are in charge of initial trauma patient management. Many private clinics are small and lack the multidisciplinary setup necessary to manage many trauma patients. This is especially true in the rural parts of the country. There is rarely a structured system in place to help junior care providers to assess and manage trauma patients and trauma patient management is not a priority in medical and nursing schools (57, 61). Research indicates that similar limitations apply to the medicines and technology building block. For example, a recent study from northwest of India showed scarce availability of many technology items for trauma care, such as equipment for airway management, blood transfusion, and imaging (62).

Decision- and policy makers in India are at least partly aware of the challenges trauma poses to the health of the country's population as well as the deficiencies in the current trauma system. In a recent judgement from the Supreme Court of India a range of measures to improve trauma systems were proposed (63). These measures focused on primary prevention and included for example an increase of fines for traffic violations, compulsory seatbelts for the driver as well as front- and back seat passengers on national highways and suspension of the driver's licence in case of drunk driving.

Furthermore, the Government of India through the Ministry of Health and Family Welfare has launched a scheme called "Capacity Building for developing Trauma Care Facilities on National Highways" (64). The objective of this scheme is "to bring down preventable deaths because of road accidents to 10 per cent by developing a pan-India trauma care network in which no trauma victim has to be transported for more than 50 kilometers and a designated trauma Care facility is available at every 100 Km.". The Indian government aims to establish 225 trauma centres, either stand alone or in existing public hospitals, along the country's major highways to a cost of more than 13 billion rupees. Four different levels of trauma centres will be established, ranging from level IV to level I centres. Whereas level I centres will mostly work as posts for ambulances, level III centres will provide initial stabilisation before transfer to a level II or I centre capable of definitive care.

The burden and epidemiology of trauma

Trauma systems have evolved as a response to a growing recognition of trauma as a threat to population health. In 1990 more than 4.3 million people died from trauma. Two years ago trauma killed almost 4.8 million people (19). About 30-50% of these deaths occur in hospital (67, 68). Although the absolute number of trauma deaths has increased during the last 25 years it is important to note that the age-standardised death rates have decreased. However, age-standardised death rates for trauma have generally fallen considerably less than for many other conditions and diseases. For example, whereas the drop in age-standardised death rates between

Table 4. Selected indicators for four lower middle income countries

	Bolivia	India	Nigeria	Ukraine
Total population (in millions)	10	1,252	173	33
GNI per capita (\$)*	1810	1260	1170	2990
Life expectancy at birth (years)	67	66	54	71
Population living in urban areas (%)	68	32	47	69
Total fertility rate (births per woman)	3.2	2.5	6	1.5
Maternal mortality ratio (per 100,000 live births)	200	190	560	23
Under 5 mortality rate (per 1,000 live births)	40	50	113	10
Vehicles (thousands)	910	114,952	12,545	14,427
Vehicle density (per 100,000 population)	9,195	9,181	7,251	43,720
Road traffic deaths (per 100,000 population)	19.2	18.9	33.7	13.5
Vehicle density (per 100,000 population)	1,615	10,274	18,836	57,429
Road traffic deaths (per 100,000 population)	21.1	18.3	17.7	9.8

Data from the World Bank Open Data and the World Health Organization Global Health Observatory Data (65, 66). No data is from earlier than 2010. *The World Bank's country classifications are based on the per capita GNI for the previous year. GNI is calculated using the World Bank Atlas method. Abbreviations: GNI Gross National Income

1990 and 2013 for communicable, maternal, neonatal, and nutritional diseases combined was 40.5%, age-standardised death rates for trauma fell by 21% (19).

In 1990, 10% of the global burden of disease estimated using disability adjusted life years (DALYs) were due to trauma. Twenty years later trauma's share of the global DALYs remained roughly the same, at 11%. During the same time period, the percentage of DALYs attributable to communicable, maternal, neonatal, and nutritional conditions was reduced from 47 to 35%. In contrast, DALYs from road traffic injury, the largest single cause of trauma mortality, increased by 35% (69). It was recently estimated that over 460 million trauma incidents occurred in 2013, up by 13% compared to in 1990 (70). Considering that the number of deaths each year is close to five million one can estimate that about 1% of trauma incidents are fatal.

Overall, falls are the most common injury mechanism, causing almost 110 million incidents, whereas transport injuries are the second most common mechanism with just over 90 million incidents (70). These global figures are reflected in population based studies from around the world, reinforcing falls as the most common injury mechanism (71-73). In contrast, facility based studies tend to report that transport injuries rather than falls predominate in people seeking medical care (74-76). Overall the numbers of falls and transport injuries have increased

substantially between 1990 and 2013, 43% and 23% respectively. The age-standardized incidence however, declined by 1% for falls and 10% for transport injuries during the same time period (70).

Evidence from both population- and facility-based studies indicates that young males carry a disproportionate large trauma burden. This finding has been replicated in population- and facility-based studies from countries worldwide, including Nepal, Sierra Leone, Rwanda, the US, Iran, Vietnam, Pakistan, Brazil, Finland, Germany, and India (71-74, 76-81). Furthermore, extremities are reported as the most commonly affected body area, followed by the head, chest and neck (71, 72). In facility-based studies the head and thorax are more commonly involved, most likely due to substantial selection bias and that such studies often are restricted to severe trauma (76, 82).

It is difficult to elicit further general points from the current trauma literature. For example, whereas studies from Uganda and Pakistan have reported people living in urban areas as having an increased risk of sustaining trauma (80, 83), studies from Sri Lanka and Ghana showed that people living in rural areas have an increased risk (84, 85). Other studies, from Sierra Leone, Nepal, and Nigeria found no difference between urban and rural areas (71, 72, 86). In other words, whereas some aspects of trauma epidemiology, such as trauma predominately being the young man's disease with substantial health and socioeconomic consequences in terms of death, disability, inability to return to work, and costs other aspects such as where the high-risk populations live are highly context-dependent (78, 87).

The burden of trauma in India

In 2013 an estimated 19% of all deaths in the world occurred in India (19). About 10% of these deaths can be attributed to trauma. This equals around one million annual trauma deaths and almost 20% of all global trauma deaths. By 2030 trauma mortality in India is projected to have increased by 30%. National epidemiological patterns largely echo global trends and road traffic injuries and falls are accountable for the brunt of trauma deaths (99, 100). Today road traffic injuries are among the top ten causes of DALYs in India, and by 2030 road traffic injuries are estimated to have climbed to be among the four biggest causes of DALYs in India (99).

Trauma research from India is relatively scarce. A substantial proportion of trauma deaths happen in urban areas (101). Although studies on where these urban deaths occur are rare available evidence indicates that hospital deaths make up almost 50% (102). Among trauma patients presenting to hospital road traffic injury and falls are the most common mechanisms of injury (103-106). Studies from Mumbai stands out from the rest as they report railway injuries as one of the top mechanisms. The high prevalence of railway injuries can likely be attributed to Mumbai's extensive network of local railways (104, 107). As in the rest of the world young males constitute the majority of trauma patients (103-106).

Current concepts in trauma management

With rapid urbanisation and increased motorisation health and trauma systems in India and worldwide need to adapt to a growing number of trauma patients. The current standard for managing trauma patients entails a systematic approach to the assessment of a patient's vital

functions and aims to combat the body's physiological response to trauma (Table 5) (Panel 2 and 3). Concepts such as the Advanced Trauma Life Support (ATLS), which build on such a structured assessment, are widely propagated worldwide (108). Today, prehospital care is also based on a similar type of initial assessment (109).

A vital component of both prehospital and hospital trauma care is systems to prioritise patients according to need and to identify patients in need of urgent and often life-saving interventions (Figure 4) (24, 41). The aim of such systems is to aid decisions on appropriate level of care and to guide further treatment. For example, many developed trauma systems include close collaboration between prehospital and hospital care providers. A typical chain of events is that the emergency medical system is alerted about an incident and an ambulance or other type of emergency vehicle is dispatched to the scene. At the scene, the prehospital care providers perform a first assessment of the individuals involved in the incident. In conducting this assessment they often use some sort of decision support system (110).

Next, the prehospital care providers call to inform the receiving hospital about the patient that they are bringing in. The hospital then has its own set of criteria to determine the level of care that the arriving patient is likely to need. These criteria also govern where the patient will be received, for example if the patient can be taken to the general emergency department and put in a cubicle or if the patient should be taken straight to the trauma resuscitation area, and the composition of the team that will receive the patient. This process is referred to as trauma team activation (111). More severe patients will typically be received by a larger team and with more specialities represented, for example anaesthesia to manage a threatened airway, compared to a less severe patients for whom other specialities than for example surgery or emergency medicine

Panel 2. The body's physiological response to trauma

Trauma constitutes an aggregate of tissue disruption, haemorrhage and coagulopathy, hypothermia, hypoxia, reperfusion insults and associated systemic responses. The body's haemodynamic response to haemorrhage occurs in two phases. First, a diminished circulating volume causes a reduction in cardiac venous return. This decrease in preload induces an increase in heart rate and peripheral vascular resistance mediated by sympathetic activity, maintaining blood pressure (113-115). Second, in haemorrhage occurring in the absence of substantial tissue disruption, as the bleeding progresses and once 20-30% of circulating blood volume is lost tachycardia and normotension is replaced by bradycardia and hypotension, mediated by vagal reflexes, ultimately resulting in syncope (116).

In trauma, bradycardia and hypotension induced by vagal reflexes is counteracted by the sympathetic activity resulting from tissue injury. Maintained tachycardia inhibits hypotension to a certain degree, however hypotension will progress if the bleeding persists (117). The sympathetic activity results in a reduction of blood flow to vital organs, potentially leading to ischemic organ injury. Haemorrhage, tissue injury, and hypoxia all induce a systemic response of the immune system (28, 118). Current research indicates that this response is biphasic, and closely connected to activation of the coagulation pathway including platelet activity prompted by bleeding (119).

First in this biphasic response comes what is called a systemic inflammatory response syndrome (SIRS) mediated by the innate immune system via various endogenous factors called damage-associated molecular patterns (DAMPs) and complement activation (120). Second, as a reaction to this pro-inflammatory part of the response the adaptive immune system is suppressed through mechanisms collectively termed the compensatory anti-inflammatory response syndrome (CARS) (121).

The systemic inflammatory response as mediated through SIRS and CARS aims to restore homeostasis. However, in the absence of successful resuscitation and sometimes in spite of correct treatment in severe trauma maladaptive coagulation resulting in coagulopathy in combination with an immune system that is running haywire, potentially aggravated by secondary insults such as surgical trauma or infection, the body break down and what is called the multiple organ dysfunction syndrome (MODS) and ultimately death ensues (122).

Panel 3. Hospital trauma care

Hospital trauma care is largely concerned with three clinical entities, namely traumatic haemorrhage, brain injury, and musculoskeletal injuries (Figure 5). Brain injury dominates as cause of death in trauma patients (123). Haemorrhage is the most common cause of preventable trauma mortality (124). Musculoskeletal injuries is the most common indication for surgery (125). A detailed account of the standards of care within each of these entities is beyond the scope of this thesis. It is interesting to note however, that substantial advancements have been made in the treatment of trauma and that many fields are experiencing shifts in paradigms.

The damage sustained by the brain in trauma to the head can be divided into primary and secondary insults. The primary insult is the direct tissue damage caused by the injury itself. The secondary insult encompasses the damages caused by tissue oedema resulting from the primary insult, as well as the effects of systemic events such as hypoxia caused by extensive haemorrhage. Through different mechanisms both primary and secondary insults lead to increased intracranial pressure and aggravation of the damage (126, 127). The treatment of traumatic brain injury, be it non-surgical or surgical, aims to reduce elevated intracranial pressure and halt evolution of the primary insult and minimise secondary insults (128).

Not too long ago the resuscitation of bleeding trauma patients relied heavily on aggressive volume replacement using mainly crystalloid fluids. However, this practice has been found to worsen trauma-induced coagulopathy, most likely through aggravating depletion of coagulation factors by diluting circulating volume (129). Today, focus is on bleeding control and damage control resuscitation including early blood transfusion (130). Damage control resuscitation also includes the concept of damage control surgery that comprises surgical haemorrhage control and temporary injury and contamination control, before the patient is shifted to intensive care for further resuscitation (131). However, with recent improvements in resuscitation practices along with worries that damage control surgery is being overused definitive surgery is increasingly performed in the first session (131, 132).

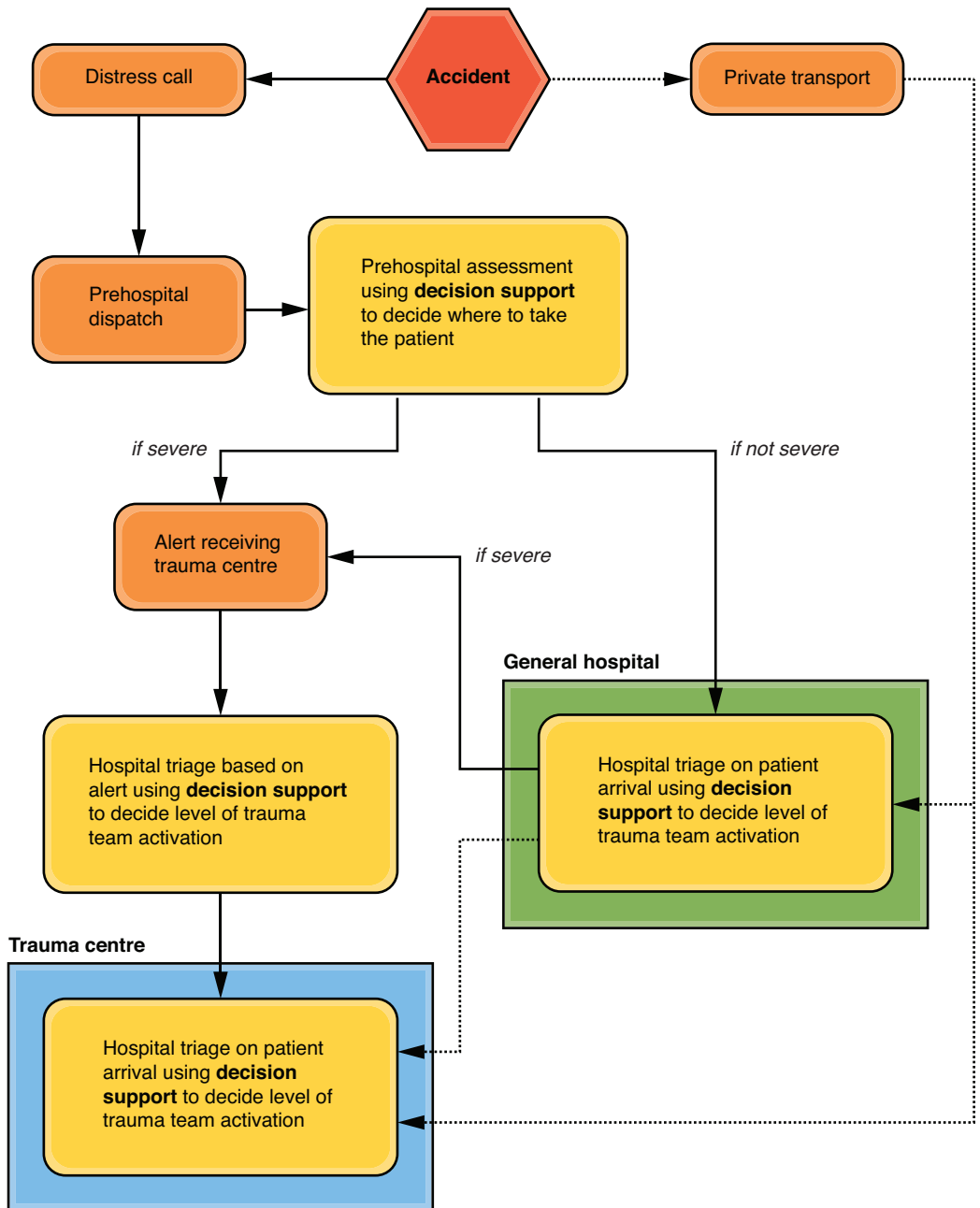
In the musculoskeletal trauma discourse there is considerable debate about when to perform early total care, i.e. definitive fracture fixation in the first surgical session, and when to perform so called orthopaedic damage control surgery, i.e. preliminary fixation in the first session (133). As resuscitation has improved the boundary between when to choose damage control over early total care has become increasingly blurred. Early total care has then been suggested as appropriate in stable patients whereas damage control should be performed in patients who are unstable or in extremis. For borderline patients some research indicate that early total care is associated with an increased risk of complications compared to damage control, although the evidence is so far limited (134, 135).

will be available on an on-call basis.

Both prehospital and hospital trauma decision support systems are generally designed for a stepwise assessment of the patient. The patient's vital signs will be assessed first. Vital signs can be defined as "the signs of life that may be monitored or measured, namely pulse rate, respiratory rate, body temperature, and blood pressure" (112). It is typically in this assessment of vital signs that trauma prediction models are used. Second, the patient will be inspected for obvious anatomical injury that need urgent treatment. Third, the mechanism of injury will be considered, as certain mechanisms entail a higher probability of occult injury or late but life-threatening complications. Finally, certain special considerations are made, for example regarding the age and comorbidities of the patient (110).

Prediction models for trauma care

As mentioned health systems are complex adaptive systems. So are trauma systems and the patients they cater to. In contrast, prediction models are not complex adaptive systems. Instead they are mechanical systems. The output of a prediction model is never a surprise provided there is no error in the input. In trauma care prediction models are prognostic, i.e. they aim to estimate a patient's risk of experiencing a specific outcome in the future. Such models are henceforth referred to as prediction models for trauma care, or only trauma prediction models.



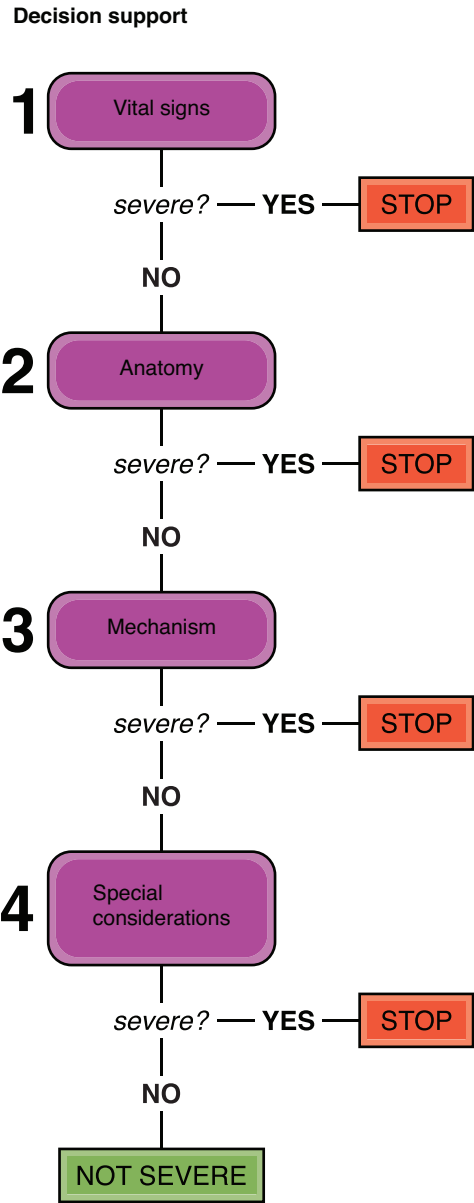


Figure 4. Outline of a trauma patient’s route from accident to hospital. The previous page and this page. The solid line with arrow heads represent prehospital transport or hospital transfer. The dotted line represents the route a patient would arrive to hospital if no prehospital care is available. The step by step nature of a decision support tool is visualised above.

In the case of trauma care and management the outcome is often death within a certain time period (25).

Trauma prediction models are generally based on vital signs and are intended to be incorporated in the first step of assessing a trauma patient (Table 6). However, prediction models for trauma care have been criticized for substantial methodological limitations and lack of validation. Furthermore, the majority of trauma prediction models have been developed in high income countries, in high resource contexts, why the applicability and relevance to low resource contexts are largely unknown (25). They also tend to include parameters that are not routinely measured in many low to middle resource trauma contexts, such as respiratory rate. In other words, there is substantial scope to improve on existing prediction models for trauma care to help strengthen trauma systems in India

Development of a valid prediction model

In medical research, there is an important distinction between explanatory research and prediction research, although these two are often confused (145). The key to the difference between explanatory and prediction research is the concept of future individuals (146). Here, future individuals refer to people belonging to a group that does not “exist” at the time of research, as they are at the other end of a temporal spectrum. For a risk factor to be considered a predictor the effect of that risk factor needs to be tested in a sample that is different from sample in which the risk factor was first evaluated.

In late 2014, Collins et al. published a statement for transparent reporting of a multivariable prediction model for individual prognosis or diagnosis, abbreviated TRIPOD (147). The need for the TRIPOD guidelines had been made obvious through a series of reviews on the methodology and reporting of prediction model studies. Prediction model studies in diabetes type 2 (148), cancer (149, 150), and traumatic brain injury (151, 152) have all been found to be of poor quality in terms of methodology and reporting. In 2012, Bouwmeester et al. reviewed

prediction model studies from all medical fields published in high impact journals and found the same thing, i.e. poor methodology and poor reporting standards (153).

Therefore, current methodological guidelines outline seven distinct steps for developing valid prediction models (7):

1. Problem definition and data inspection
2. Coding of predictors
3. Model specification
4. Model estimation
5. Model performance
6. Model validation
7. Model presentation

The first step of defining the problem and inspecting the data includes framing the research question and deciding if the aim is to identify predictors, to generate predictions, or both. If the aim is to generate predictions then the output will often be a model, i.e. a combination of predictors that can be used to obtain an estimate of the probability of a specific outcome in a particular future individual (8). This first step also involves choosing the candidate predictors, i.e. the variables from which the main effects to be included in the final model will be chosen,

Table 5. A structured assessment of a trauma patient's vital functions

Mnemonic	Function	Items to assess	Relevant vital signs	Life threatening conditions
A	Airway with cervical spine protection	Listen for voice and breathing sounds. Inspect the oral cavity for foreign bodies. Apply cervical spine protection if there is reason to suspect cervical spine injury	-	Threatened airway, for example due to severe facial swelling, airway trauma, loss of consciousness
B	Breathing	Inspect chest wall movements. Auscultate lungs.	Respiratory rate, blood oxygen saturation	Tension pneumothorax
C	Circulation	Palpate central and peripheral pulses. Palpate abdomen and pelvis.	Heart rate, blood pressure, capillary refill	Critical bleeding from the thorax, abdomen, pelvis, large bones. Cardiac tamponade
D	Disability	Perform a rapid neurological examination.	Level of consciousness (Glasgow coma scale)	Intracranial bleeding
E	Environment	Undress the patient, look for signs of injuries. Log roll and inspect and palpate trunk and spine. Perform a rectal examination.	Body temperature	

Partly adapted from Thim et al. (136)

and inspecting the data that will be used for deriving the model including how variables were defined and data completeness (154).

Once the research question has been formulated and the candidate predictors chosen it is time to decide how to code these variables. Variables are either categorical (nominal, ordinal, or interval) or continuous (155). In its most basic form a categorical variable has only two categories and is then referred to as dichotomous or binary. Some variables are by nature dichotomous, like death. However, most are not. For example, smoking can be expressed as a dichotomous variable, i.e. with only yes or no as possible answers, but can also be expressed as the number of cigarettes smoked in a day, a week, or per month.

Variables like age, blood pressure, and weight are continuous. A common, but questionable, practice in prediction research is to categorise continuous variables (156). For example, age may be categorised as <15 years, 15-55 years, and > 55 years. The reasons for doing this vary but often the aim is to simplify otherwise complex associations. The current consensus is to avoid categorising continuous variables at least initially (157), and to use methods for flexible modelling of potential non-linear associations between candidate predictors and the outcome (158, 159).

The next steps involve deciding the modelling method and choosing what variables to include in the final model. Logistic regression has been referred to as the most common modelling method (7). To decide on which variables out of all possible candidate predictors to include the recommendation is to use a combination of subject matter knowledge and data driven selection

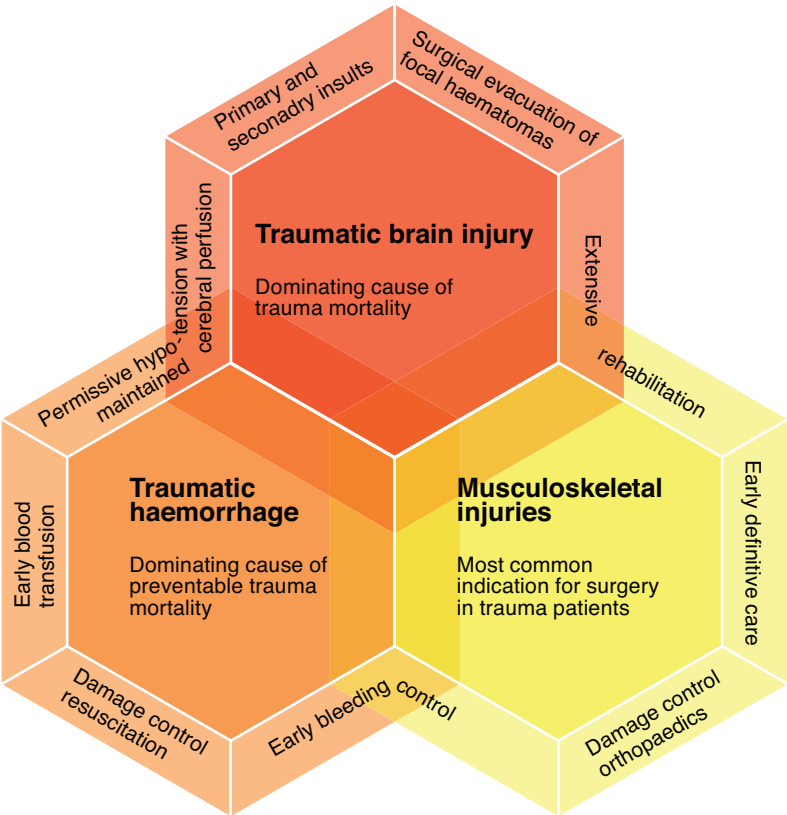


Figure 5. Outline of the three major clinical entities. Includes key concepts within each field and how these may overlap

methods (160). There is no general agreement on the best method for data driven selection of predictors, but stepwise selection algorithms are perhaps the most widely used (161). Such algorithms use an iterative process guided by statistical tests to identify the model that fits the data the best (162). This approach has inherent problems, especially relating to the stability of the variables included in the final model and the size of regression coefficients.

A stable model is robust to changes both in terms of study sample, provided these samples are drawn from the same population, and selection algorithm (163). In other words, the predictors included in the final model should be the same even if a new population sub-sample is used to derive the model or if a different selection algorithm is employed. This issue is particularly prevalent when stepwise selection algorithms are used in small datasets, as the risk of including so called noise or redundant variables increases when the sample size is small. To improve stability of models derived using stepwise selection algorithms in small datasets the use of resampling techniques and a flexible approach to significance levels are recommended (164).

Resampling techniques allow for simulation of model derivation in new population sub-samples and stability can hence be formally tested (165). The flexible approach to significance levels entails a focus on the effective sample size rather than total sample size. In modelling with a dichotomous outcome the effective sample size is equal to the number of observations with the outcome (166). An observation with the outcome is termed an event and in general a minimum of ten events per candidate predictor is recommended as sample size if the standard significance level of 0.05 is used. In smaller datasets the significance level for variable inclusion may need to be substantially higher to avoid missing important associations.

Another problem that arises particularly often when stepwise selection algorithms are used in small datasets is so called overfitting. This issue has important parallels to the discussion on the difference between explanatory and prediction research. Overfitting refers to models that fit the data used to derive the model too well, resulting in predictions that are too extreme when the model is tested on future individuals (167). To combat this problem there are multiple techniques available, all aimed towards reducing the size of the regression coefficients (168). This active reduction of regression coefficients is termed shrinkage and may be incorporated into the estimation method or applied after estimation has been performed using specific techniques to calculate a shrinkage factor.

Once the model has been derived the performance of the model has to be tested. Performance here refers the overall predictive performance of the model, although no widely accepted measure for such performance exists. Instead, it may be more useful to discuss measures of different performance aspects. The final model needs to be evaluated both in the dataset used to derive the model but also in a dataset external to this dataset (169). The evaluation performed in the derivation dataset is called internal validation whereas the validation in an external dataset is called external validation. In the pragmatic spirit of prediction research it has been argued that external validity is all that matters (170), i.e. as long as a model works it does not really matter how it was derived or how it performed in the original data.

To evaluate a prediction model several measures have been proposed. In general, they fall within one of three domains of performance measures, i.e. discrimination, calibration, and clinical usefulness. Discrimination refers to the ability of a prediction model to differentiate between individuals with and without the outcome. A model with good discrimination has a

wider spread between predictions and a limited overlap between patients with and without the outcome (171). Calibration refers to the agreement between predicted and observed outcomes. Because the predicted probability of the outcome in an individual ranges between 0 and 1 whereas the observed outcome in the same individual can be only 0 or 1 calibration has to be assessed on group level. A common approach is to divide the study sample into ten groups using deciles of predictions and then compare the predicted proportion of patient with the outcome with the observed proportion in each group (172).

The last domain of predictive performance is clinical usefulness. This domain is only relevant for models aimed to guide clinical treatment decisions, such as trauma prediction models. Although for such models it can be argued to be the most important domain it was not until quite recently that objective and easily quantifiable measures were proposed (173). The suggested method to estimate clinical usefulness is called decision curve analysis and aims to establish whether using a model may lead to better decisions (174). This focus on clinical usefulness is closely associated with the last model development step of model presentation. To be useful a model needs to be easy to use and many different formats exist. Traditionally models were presented as paper based score charts or nomograms but today it becomes increasingly common to publish models as interactive smartphone or online applications (140).

Table 6. Examples of trauma prediction models

Model (reference)	Target setting	Target population	Predictors	Outcome
CRAMS (137)	Prehospital	General trauma	Circulation, Respiration, Abdomen, Motor, Speech	Hospital mortality or major surgery
GAP (138)	Hospital	General trauma	GCS, cAge, cSBP	Hospital mortality at discharge, mortality in the emergency department or during surgery
MGAP (139)	Prehospital	General trauma	GCS, cSBP, MOI, cAge	Hospital mortality
Perel (140)	Hospital	Patients with traumatic	GCS, Age, SBP	Hospital mortality within 28 days after injury
PHI (141)	Prehospital	bleeding	cSBP, cHR, cRR, LOC	Hospital mortality, emergency surgery
PSS (142)	Prehospital	General trauma	cSBP, cRR, LOC	Prehospital or hospital mortality
RTS (143)	Prehospital	General trauma, aged > 14 years	cSBP, cRR, cGCS	Hospital mortality
KTS (144)	Hospital	General trauma	cSBP, cRR, LOC, Number of serious injuries	Composite of mortality and need for hospital admission

Abbreviations: c Categorised, GCS Glasgow Coma Scale, HR Heart Rate, LOC Level Of Consciousness, MOI Mechanism Of Injury, RR Respiratory Rate, SBP Systolic Blood Pressure

Rahul was meeting up with some friends in Bandra, down by the water just off Mount Mary. Doubtlessly one of the best places to hang out in this part of Mumbai it was a popular place among the city's younger crowd. Humanity was thick as he crossed through Dharavi on his bike, a blazing matte black Bullet 500 with a 499 cc single cylinder engine. Rahul quickly put on the helmet as the traffic came to a complete halt just after the bridge over Mithi River and before the police officer waving frenetically to control the oncoming horde could catch him without wearing it. When it was his turn, he speeded over the crossing and as soon as he pushed onto the Western Express Highway he removed his helmet again.

Traffic was less heavy here and Rahul was soon travelling at some 80 kilometres per hour. With his shirt open down most of the front and no helmet on the wind gushing through his hair was a welcome exchange from the suffocating Dharavi air. He loved this, the speed, the thrill, the adrenaline. Closing his eyes for a second was all it took for him to miss the car overtaking him on the left and suddenly the crash was inevitable. Rahul would never know what happened next. As he lay limp on the roadside nearby crowds quickly gathered by his side. Soon, two police officers posted at a nearby crossing were alerted by the commotion and came over. They dragged Rahul into their car and drove off to Sion Hospital.

With heavy traffic the drive took almost an hour and the police entered through the hospital gates about 90 minutes after the accident. They honked their way through the crowds, taxis, and bikes parked outside the casualty building and then pulled him out of the car, put Rahul on a metal trolley, and wheeled him into the casualty department. Inside it was just as busy as outside, with throngs of people waiting to be assessed by the casualty officer and guided to medicine, surgery, or orthopaedics for further evaluation. Soon enough the police managed to get hold of the casualty officer, who quickly recognised the seriousness of the situation.

Rahul was immediately taken to the resuscitation area located behind several double swing doors with signs urging relatives to keep out. This was a room with a floor area of about 30 square meters, just another double swing door from a dedicated trauma intensive care unit with fourteen beds. No one had been warned about Rahul's arrival and when he was pushed into the room the team of four residents, two from surgery and one from anaesthesia and orthopaedics respectively were all busy with another patient. Two nurses were sitting behind a wooden desk covered with papers in the far end of the room. One of the surgical residents shifted to Rahul's trolley and started a primary survey.

Rahul was not unconscious but his level of consciousness was definitely altered. He had obvious open fractures of his left forearm and lower leg but there were no signs of ongoing catastrophic bleeding from these sites. As the resident completed the primary survey she found a patent airway. She auscultated bilateral breath sounds. When she connected Rahul to the pulse-oximeter it showed a blood oxygen saturation of 72%, which she determined was an incorrect reading and therefore planned for an arterial blood gas later. She found palpable peripheral pulses, a heart rate of 95 beats per minute and a systolic blood pressure of 110/80 mmHg. Rahul groaned when she palpated his abdomen, but he was not obviously distended and there were no other signs of peritonitis. His pelvis was stable.

ntic case

Throughout this first part of the survey Rahul held his eyes closed. The resident pressed hard with her thumb just above his right eyebrow and Rahul opened his eyes reluctantly, mumbled something that was only partly intelligible, and made a weak attempt to remove the resident's hand. As she removed the pressure Rahul closed his eyes again and his hand fell to his side. She did the math, $2+3+5$, Rahul's level of consciousness according to the Glasgow coma scale was 10. Finishing the survey she found no evidence of skeletal injury in addition to his open fractures and besides multiple abrasions and contusions there were no evident major soft tissue injury.

The resident quickly summarised her findings, quietly because the second surgical resident was busy trying to place a urinary catheter on the other patient and the orthopaedic resident was stuck putting direct pressure to the bleeding remnants of the same patient's left lower limb. The anaesthesia resident was ventilating the patient using a bag-valve device. Rahul had a patent airway and was circulatory stable. There was abdominal tenderness and his level of consciousness was altered. She was keen to perform a bedside ultrasound as well as plain pulmonary and pelvic x-rays before further imaging was undertaken. Unfortunately, the portable ultrasound machine was broken. The x-rays revealed nothing much. She therefore sent Rahul to the computed tomography facility and forgot to do the arterial blood gas.

This place was located four buildings away, and the only way to get there was by pushing the trolley outside. Luckily, it did not rain. An intern, in her last year of medical school, got to accompany Rahul on the way there along with a ward boy doing the actual pushing. They got him through the crowds moving around inside the compound. Once they got there they had to wait for another scan to finish before it was Rahul's turn. He underwent the investigation and they pushed him back to the resuscitation area. Once there he was put in a corner and the intern reported to the same surgical resident who earlier performed the survey. She went over to Rahul and pinched him again. This time there was no response. She quickly started a new survey. Rahul's breathing was now obviously obstructed, the systolic pressure was 70 mmHg, and Rahul's heart rate had increased to 120 beats per minute.

While the anaesthesia resident intubated Rahul the surgical resident called the senior surgeon on call. It took the senior surgeon, who was busy in another part of the hospital, 15 minutes to get to the resuscitation area. Once there, she made the decision to perform an explorative laparotomy why Rahul was rushed to the adjacent operating room. She identified bleeding from the liver and spleen and therefore packed his abdomen to temporarily arrest bleeding and allow for additional resuscitation. After surgery he remained on ventilator. Blood arrived when the paperwork was done, about 90 minutes after he arrived to the hospital, and transfusion was started. Unfortunately the amount of blood products they received was much less than what they had asked for. Two hours after surgery, when he lay in the trauma intensive care unit, he deteriorated again. Additional resuscitation attempts were futile and Rahul was soon declared dead.



study rationale and aim

Trauma is one of the top threats to population health globally. Health systems increasingly need to adapt to a growing burden of trauma. A striking disparity in global trauma mortality exists with the brunt of deaths occurring in low- and middle income countries. In many high income countries trauma mortality has been successfully reduced through the implementation of trauma systems. Trauma systems in low- and middle income countries are still in their infancy. India alone accounts for 20% of global trauma mortality and a substantial proportion of these deaths occur in urban areas. India's trauma systems have repeatedly been referred to as immature. Hence, interventions and innovations that can help strengthen India's trauma systems are urgently needed.

One of the most important components of a successful trauma system is a structured approach to the assessment and management of trauma patients. A systematic assessment is vital to guide decisions on treatment as well as level of care. Prediction models can aid this assessment by giving care providers an estimate of prognosis. Currently available prediction models have been criticised for methodological shortcomings and many include parameters that are not routinely measured in Indian hospitals. Therefore, the aim of this research was to develop a model for prediction of trauma mortality in urban Indian hospitals.

Specific objectives

- I.** To assess if early mortality in trauma patients has changed over time in a public university hospital in urban India
- II.** To derive a vital signs-based prediction model for early mortality among adult trauma patients in three university hospitals in urban India
- III.** To validate a vital signs-based prediction model for early mortality among adult trauma patients in three university hospitals in urban India, and to compare it with existing models for use in early trauma care
- IV.** To assess the transferability of vital-signs based prediction models between an urban Indian trauma context and a trauma context in the US

methods

Design and context

The basis for most work presented in this thesis was a prospective multicentre observational cohort project called Towards Improved Trauma Care Outcomes in India, mostly referred to using the acronym TITCO, or TITCO India. The driving force behind TITCO was to establish the first multi-centre trauma registry in India. At the time of writing, four hospitals across urban India participate in TITCO, but the data used for this thesis is only from three of these hospitals. The rationale for including three centres was that these centres were the first three to obtain ethical clearance and data collection was initiated at approximately the same time in all three centres. The TITCO data used for this thesis was collected between October 1, 2013, and July 23, 2014 [II-IV] (Table 7).

The centres included were Lokmanya Tilak Municipal General Hospital in Mumbai (LTMGH), Jai Prakash Narayan Apex Trauma Center in Delhi (JPNATC), and Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital in Kolkata (SSKM). Whereas these three centres are similar in the sense that they are all public university hospitals and tertiary referral centres located in three of India's most populated cities, the level of trauma care provided differs substantially between centres. The rationale for selecting these specific centres was their geographical spread, that they were located in major cities, and that they were university hospitals with prerequisites for research. Along the spectrum of different trauma contexts the centres ranged from low to middle resource trauma contexts.

According to official figures LTMGH has more than 1400 beds and more than 60,000 admissions per year. It is situated in central Mumbai, close to major highways and local railways. As such, traditionally most of the Mumbai road traffic and railway trauma was brought to this centre and as a result it was one of the first centres in India to open a dedicated trauma ward. Today, this ward is located in the same building as the general casualty and has 14 beds. It functions as a trauma intensive care unit but out of 14 beds only six to eight has usually working ventilators.

Just outside the ward is a trauma receiving and resuscitation area, where trauma patients are managed only minutes after arriving to the hospital. Connected to both the resuscitation area and the ward is an emergency operating theatre where most of the acute interventions are performed. A general surgery residents and an anaesthesia resident staff the ward and resuscitation area. Other specialities as well as senior competence in general surgery and anaesthesia are available on an on-call basis. Nurses are posted in both the ward and resuscitation area but take less part in early patient management. X-ray and ultrasound are available in the resuscitation area itself, whereas the computed tomography facility is located four buildings away. After discharge from the trauma ward, patients are managed in the general surgery, orthopaedic, and neurosurgical wards as appropriate.

In Delhi, JPNATC is part of All India Institute for Medical Sciences (AIIMS), although it is designed as a standalone trauma centre situated away from the main AIIMS hospital. It has about 180 dedicated trauma beds. Patients are first received and triaged to green, yellow, or red areas according to severity where they are then managed and resuscitated as appropriate. Residents from general surgery, orthopaedics, neurosurgery, and anaesthesia are posted in the resuscitation area around the clock. Nurses are trained to actively participate in early trauma

management. Operation rooms are available in the immediate vicinity of these areas, as are facilities for X-ray, ultrasound, computed tomography, and magnetic resonance imaging.

In Kolkata, SSKM is the only public tertiary centre that provides neurosurgery. As such it receives referred neuro trauma patients from all of Kolkata and surrounding areas. The hospital has more than 1500 beds. As opposed to LTMGH and JPNATC, SSKM has no dedicated trauma beds. It has a general emergency department where all emergencies, regardless of cause, are seen. In the emergency department there is no area for resuscitation of trauma patients. The emergency department is staffed by surgical residents and interns with senior expertise being available on an on-call basis. Nurses generally do not take active part in early management of trauma patients. X-ray, ultrasound, and computed tomography facilities are available in the same building as the emergency department. In all three hospitals the patient fee is nominal.

Table 7. Overview of the studies included in this thesis

	Study I	Study II	Study III	Study IV
Design	Observational single-centre, retrospective cohort	Observational multi-centre, prospective cohort	Observational multi-centre, prospective cohort	Combination of observational multi-centre prospective cohort and retrospective registry-based analysis
Objective	Assess temporal trends in early mortality	Derive a model for prediction of early mortality in adult trauma patients	Validate a model for prediction of early mortality in adult trauma patients	Assess transferability of prediction models for early mortality in adult trauma patients
Data sources	Three cohorts of patients admitted to the same public university hospital in Mumbai	Adult trauma patients admitted to three public university hospitals in Mumbai, Delhi and Kolkata (TITCO)	TITCO	TITCO and adult trauma patients admitted to hospital in the US (NTDB)
Data collection periods	1998, 2002, and 2011	October 2013 - January 2014	January 2014 – July 2014	October 2013 – July 2014 (TITCO), 2012 (NTDB)
Main analysis methods	Multivariate logistic regression	Multivariate logistic regression with stepwise selection of main effects. Analyses of discrimination and calibration	Multivariate logistic regression with stepwise selection of main effects. Analyses of discrimination and calibration. Decision curve analysis	Multivariate logistic regression with stepwise selection of main effects
Outcome	Early mortality			
Main variables of interest	Cohort/year, age, sex, anatomical injury severity	Systolic blood pressure, heart rate, Glasgow coma scale		

Abbreviations: NTDB National Trauma Data Bank, TITCO Towards Improved Trauma Care Outcomes in India

The design of study I differed from that of study II-IV as it was a retrospective analysis of three cohorts of patients admitted to LTMGH during 1998, 2002, and 2011. Study IV was a combination of the above outlined prospective cohort project and a registry based analysis of the U.S. National Trauma Data Bank (NTDB), which includes data from trauma centres all over North America (175). Participation is voluntary even though the American College of Surgeons encourage centres to participate. Hence, also the NTDB should be described as a convenience sample. In the complete NTDB dataset there are more than 5,000,000 observations from more than 900 hospitals. Researchers may buy access to the NTDB from the American College of Surgeons (ACS). For this thesis, data from 2012 was used, as that was the latest data available.

Data and eligibility criteria

As study I included data from cohorts of patients admitted to LTMGH during 1998, 2002, and 2011, these datasets were collected before this research was initiated. The rationale for using these datasets despite that they were collected for other research and can rightly be described as very heterogeneous was that even single centre studies spanning almost fifteen years from India were lacking. To retrospectively gather this data was deemed to be a close to impossible undertaking, as the patient records are all paper based and given enough time the Indian humid air tend to destroy such things.

All three cohorts were collected for purposes of other studies than this thesis, and were hence not standardized in terms of the variables included in each dataset. The 1998 cohort was collected between January 1, 1998, and December 31, 1998. All patients admitted to the trauma ward at LTMGH were included. The surgical resident currently on duty collected data on patient demographics, mechanism of injury, level of consciousness, injuries, and mortality within 24 hours of admission. Injury details were captured from the patient record, using notes, x-ray and computed tomography reports, as well as surgical notes.

Similarly, the 2002 dataset was also collected by the surgical resident currently on duty and included all patients admitted to the LTMGH trauma ward between August 1, 2001, and May 31, 2002. Largely the same variables were collected as in the 1998 dataset and the sources of injury details were the same. Also, the length of follow up was the same in the 2002 dataset as in the 1998 dataset, i.e. discharge or death was recorded 24 hours after admission. The 2011 cohort was collected for a trauma project conducted with WHO. For this project a dedicated project officer was employed to perform data collection. She worked day, evening, and night shifts according to a randomized schedule, so that the patients admitted during her shifts constituted a random, representative, sample compared to the all patients admitted. Each shift was eight hours and she worked five days a week. For patients admitted outside her shift she extracted data from patient records.

The 2011 cohort included all patients with life or limb threatening injuries, defined using a list of injury mechanisms in combination with certain physiological signs, such as hypotension. In practice, the 2011 cohort included all patients admitted to the LTMGH trauma ward, which excludes patients with minor abrasions and cuts, as these would be managed in the general surgical emergency department, and isolated limb injuries conventionally managed in the orthopaedic emergency department. In addition to the data included in the 1998 and 2002

datasets, the 2011 dataset also included data on length of hospital stay, length of intensive care unit stay, and procedures and investigations performed. Patients were followed up until discharge or death, whichever occurred first.

The procedure for data collection in TITCO was similar to that of the 2011 cohort. Eligible for inclusion were all patients aged 15 years or older with history of trauma. Patients with isolated limb injury, i.e. extremity fractures without associated vascular injury, were not included. One project officer was employed for each centre. The project officers worked shifts that were eight hours long. They worked day, evening, and night shifts so that all possible shifts were covered during the course of a month. For patients admitted during their shifts they observed patient resuscitation and collected data from patient records. If a parameter was not recorded or not documented during their observation, they were allowed to inquire about it from the resident or nurse on duty. For example, if a blood pressure was recorded but not documented, they would ask about it.

For patients admitted outside their shifts the project officers extracted data from patient records. Patients were followed up until death or discharge. Data was first entered on a paper intake form, on which both the patient indoor number as well as study ID was recorded. The data was then entered from the paper intake form to a Microsoft Excel database using an interface that looked exactly the same as the intake form. The indoor number was not entered into the electronic database and therefore this database can be considered as de-identified. Each patient was first entered into the electronic database 24 hours after admission, along with all the parameters collected for this time period. This record was then retrieved and the remaining parameters entered when the patient was discharged or died, provided he or she did not do so earlier than 24 hours after admission.

The electronic database from each hospital was then uploaded to a central database. Datasets from all hospitals were collated into a single database on a weekly basis. There were three quality control mechanisms used. First, each week all data was checked for consistency and potential errors were sent back to the project officers and their supervisors for checking. The project officers then cross checked the data entered into the database with their paper formats and if necessary with the original patient record. They then updated the electronic database by retrieving and re-submitting the previously entered observation. Raw versions of the weekly datasets have been stored.

Second, the data was discussed at weekly online teleconferences. During these calls members from project management as well as all the project officers participated. Third, on-site quality control has been conducted on two occasions. This was performed by randomly selecting a number of observations from the complete databases. The project officers were then requested to retrieve the paper intake format as well as the original patient record for each of the selected study IDs. The electronic entries, paper forms, and original records were then checked for consistency. No major inconsistencies were observed. Hence, it can be said that the data is as good as the data in the original patient records and as such are representative of routine recordings.

The NTDB dataset used in study IV included data on patients admitted to trauma centres in North America during 2012. Each year, the ACS has a call for data, a time period, when all participating hospitals are asked to submit data from the previous year. The data is from each

hospital's local patient registry and as such consist of routine recordings. Although the ACS encourage hospitals to adopt the standards and variable definitions used in the NTDB many hospitals do collect additional data points, and the variables and how the variables are coded may differ between hospitals. This potential issue has been solved by mapping local variables and codes to their appropriate NTDB counterparts. According to American legislation the NTDB is a so-called limited dataset meaning that it does not include information to identify individual patients.

Variables

The outcome variable in all studies was early mortality. It was not possible to keep the definition of early mortality exactly the same across all four studies. Because the focus of this thesis was prediction of early mortality using vital signs, the most reasonable and clinically useful definition would be death in hospital within 24 hours from the time when the vital signs were recorded. This definition was used in study II-IV. For study IV, the date and time when vital signs were recorded were not available in the NTDB dataset. Hence, for the NTDB dataset, early mortality was defined as death in hospital within 24 hours of arrival to hospital. In study I, early mortality was defined as death in hospital within 24 hours from admission to hospital. The rationale for choosing early mortality as the outcome was that a high risk of early mortality indicates a need for acute or urgent intervention, as opposed to mortality within a longer time span (2, 3).

The main variables of interest, in addition to the outcome, differed slightly between studies. In study I, the focus was on the temporal trend in early mortality and other variables were used to describe the samples and to adjust measures of mortality. Age, sex, mechanism of injury, as well as injury severity was used. Age was defined as a categorical variable using internationally accepted cutoffs. Injury severity was estimated using the international classification of disease injury severity score (ICISS). This score is a so-called anatomical injury severity score, known to outperform more conventional scoring systems such as the injury severity score (ISS) (176, 177).

As the name implies, ICISS is based on the international classification of disease (ICD) codes. Each code is assigned a survival risk ratio (SRR) that is equal to the proportion of patients with a specific ICD-code who survived in a reference population of patients. Hence, a SRR can range between 0 and 1, with 0 indicating that no patient with that specific code survived, and 1 indicating that all patients with that specific code survived. The final ICISS can then be calculated as the product of all of a patient's SRRs. It can also be equal to the SRR of the single worst injury, i.e. the injury with the lowest SRR (178). The ICISS is interpreted as the probability of survival, meaning that a patient with an ICISS of 0.2 has a 20% probability of survival whereas a patient with an ICISS of 0.8 is estimated to have an 80% probability of survival. Major trauma was defined as $ICISS < 0.9$ (179).

The injuries of all patients in each of the 1998, 2002, and 2011 cohorts were coded according to ICD-10. Each code was then assigned an SRR according to the procedure outlined above and the final ICISS was calculated using the single worst injury approach. Conventionally, studies with large samples use the study population to estimate SRRs and calculate ICISS. Smaller studies may instead use SRRs published from other reference populations. The SRRs were calculated based on the Study I sample and later used to estimate ICISS, bearing in

mind the potential same sample bias introduced in this way. However, we were unable to find published SRRs from an appropriate reference population and instead resorted to this more explorative approach.

In study II-IV, age, sex, mechanism of injury, and whether the patient was transferred from another hospital were used to describe the study populations, in addition to the three vital signs of interest. These were systolic blood pressure, measured in mmHg, heart rate as beats per minute, and Glasgow coma scale. Glasgow coma scale is a measure a level of consciousness and range from 3 to 15. The total score is a composite of three components, an eye component, a verbal component, and a motor component. The eye component range from 1 to 4, the verbal component from 1 to 5, and the motor component from 1 to 6. The final score is the sum of these three components (180).

A Glasgow coma scale of 3 means that the patient has no eye movement and has no verbal or motor responses, even to pain. In contrast, a score of 15 indicate a fully conscious patient. A patient with so severe facial swelling that it prevents evaluation of eye response is assigned an eye component of 1c, and a patient with an intra-tracheal tube preventing assessment of the verbal response is assigned a verbal component of 1t. When totalling the Glasgow coma scale a patient with an eye component of 1c but with normal verbal and motor responses would get a score of 12c, whereas a patient with a verbal component of 1t but normal eye and motor responses would get a total score of 11t. I treated an eye component of 1c as equal to 1 and a verbal component of 1t as equal to 1. This is not conventionally done, and the rationale for doing it here was as to simplify the final assessment.

Of course, there are many more vital signs than systolic blood pressure, heart rate, and Glasgow coma scale. In addition to these three the most common include respiratory rate, body temperature, blood oxygen saturation, and capillary refill time. They have all been shown to be associated with trauma mortality (181). The rationale for focusing on systolic blood pressure, heart rate, and Glasgow coma scale was that these three are the vital signs most extensively used in the study context. No claim that these are the most prognostic is made and no tests to compare their prognostic value with other vital signs were conducted before the onset of this thesis work.

Analyses and statistical methods

The statistical software Stata (StataCorp, Texas, USA) was used for all statistical analyses. In study I, the main analysis model was a logistic regression with early mortality as the dependent variable and cohort as the independent variable. In further analyses we adjusted for sex, age, mechanism of injury, and anatomical injury severity. Subgroup analyses were conducted in females, males, patients aged less than 15 years, between 15 and 55 years, and patients aged more than 55 years, in patients with fall, railway injury, road traffic injury, and assault, patients with major trauma, and patients with minor trauma.

In study II the focus was to derive a model for predicting early mortality. This was done using logistic regression with early mortality as the outcome. In practice, this model uses the logistic function (Equation 1) to estimate a probability of early mortality using the linear combination of the model intercept, coefficients, and candidate predictors (Equation 2), henceforth referred to as the linear predictor.

(1)

$$f(x) = \frac{1}{1 + e^{-x}}$$

(2)

$$x = \beta_0 + \sum_{i=1}^n \beta_i \omega_i$$

where β_0 is the model intercept, β_i the coefficient of the independent variable ω_i and n the number of independent variables.

Restricted cubic splines were used to model potential non-linear associations between the candidate predictors and early mortality log odds. Restricted cubic splines are piece-wise polynomials that allow the strength and direction of the association to vary across the continuum of a variable (158). The degree of flexibility is decided by the number of points at which the association is allowed to change direction. These points are called knots. The term restricted indicates that the associations modelled using this type of spline are restricted to be linear before the first knot and after the last knot. In restricted cubic splines, the change in association follows a cubic distribution and hence the transition between two points is smooth.

Conventionally, three to seven knots are used, positioned at equally spaced percentiles.

The number of knots determines the number of spline basis functions, i.e. the number of parameters resulting from transforming the variable into a restricted cubic spline, here denoted n . For each observation, let B denote the original variable and B_i the i :th spline basis function, where $i \in \{1, \dots, n-1\}$. Then, let k_i denote the value of B at the position of the i :th knot and $i \in \{1, \dots, n\}$ (Equation 3 and 4).

(3)

$$B_1 = B$$

(4)

$$B_{i+1} = \frac{(B - k_i)_+^3 - (k_n - k_{n-1})^{-1} \left[(B - k_{n-1})_+^3 (k_n - k_i) - (B - k_n)_+^3 (k_{n-1} - k_i) \right]}{(k_n - k_1)^2},$$

$$i \in \{1, \dots, n-2\},$$

$$(u)_+ = \begin{cases} u, & \text{if } u > 0 \\ 0, & \text{if } u \leq 0 \end{cases}$$

A stepwise backward selection algorithm that started with the most complex model was designed. To determine the most complex model departures from the linearity assumption were first assessed using lowess regression. Variables for which evidence of non-linearity was found were introduced in the model as restricted cubic spline transformations with four knots placed at equally spaced percentiles. Variables without evidence of non-linearity were introduced as linear terms.

Considering that the candidate predictors were systolic blood pressure (*sbp*), heart rate (*hr*), and Glasgow coma scale (*gcs*) the hypothetically most complex model with early mortality log odds, denoted γ , as the dependent variable would include three spline basis functions for each of these variables (Equation 5).

(5)

$$\gamma = \beta_0 + \sum_{i=1}^3 \left(\beta_{sbp_i} sbp_i + \beta_{hr_i} hr_i + \beta_{gcs_i} gcs_i \right)$$

where β_0 is the intercept, β_{sbp_i} is the coefficient of the i :th spline basis function of *sbp* and so on.

The spline basis functions belonging to the same candidate predictor, each defined as a free parameter in the model, is henceforth referred to as a predictor's transformation.

The significance of transformations was tested using a joint test of all coefficients being simultaneously equal to 0. If any transformation had a p-value ≥ 0.2 this transformation was removed from the model. If the number of knots of the removed transformation, n , was > 3 the original variable was retransformed using $n-1$ knots. This new transformation was then introduced into the model and the estimation procedure was repeated.

If more than one transformation had a p-value ≥ 0.2 the transformation with the highest p-value was removed. In the event of a transformation with three knots not being significant the transformation was replaced by the original variable as a linear parameter. If the linear parameter was not significant the variable was removed from the model altogether. The selection algorithm terminated when all included transformations or linear parameters had a p-value < 0.2 .

A bootstrap procedure was used to select stable parameters, internally validate the model, and to estimate a linear shrinkage factor that was applied to the coefficients of the parameters included in the final model to counter overfitting. First, 300 bootstrap samples were drawn with replacement. These bootstrap samples were of the same size as the original sample. In each bootstrap sample the selection algorithm outlined above was used to come up with a bootstrap model. Let M_s denote the model derived in each bootstrap sample, where $s = \{1, \dots, p\}$, p is the number of bootstrap samples and M_0 is the model derived in the original, not bootstrapped, sample. Solving x for M in Equation 2 we get (Equation 6):

(6)

$$M_s = \beta_{0,s} + \sum_{i=1}^n \beta_{i,s} \omega_{i,s}$$

To include stable parameters in the final model only parameters that were selected in M_0 as well as in at least 50% of bootstrap models were included. Internal validation was performed by estimating the optimism in selected predictive performance measures. Let $A_{s,s}$ be the value of a specific predictive performance measure when model M_s is evaluated in bootstrap sample s and $A_{s,0}$ be the value of the same predictive performance measure when model M_s is evaluated in the original sample.

Using M_s to predict γ in the original sample can be expressed as (Equation 7):

(7)

$$\gamma_{s,0} = \beta_{0,s} + \sum_{i=1}^n \beta_{i,s} \omega_{i,s}^0$$

where $\gamma_{s,0}$ is the predicted early mortality log odds in the original sample obtained using the intercept $\beta_{0,s}$ and coefficients $\beta_{1,s}, \dots, \beta_{n,s}$ estimated in bootstrap sample s . $\omega_{i,s}^0$ denotes the parameters selected in bootstrap sample s applied in the original sample.

Optimism, denoted O , was then defined as (Equation 8):

$$(8) \quad O = \frac{\sum_{s=1}^p (A_{s,s} - A_{s,0})}{p}$$

Finally, the linear shrinkage factor was calculated by using each $\gamma_{s,0}$ as the independent variable in a logit regression with γ as the dependent variable, i.e. (Equation 9):

(9)

$$\gamma(\gamma_{s,0}) = \beta_0 + \beta_1 \gamma_{s,0}$$

and then the linear shrinkage factor, denoted sf , was defined as (Equation 10):

$$(10) \quad sf = \frac{\sum_{s=1}^p \beta_{1,s}}{p}$$

The predictive performance measure used to estimate optimism in Study II was the area under the receiver operating characteristics curve (AUROCC). The AUROCC is a measure of discrimination, i.e. how well a model discriminates between patients with and without the outcome. The measure ranges between 0 and 1, with 1 indicating perfect discrimination and 0.5 indicating discrimination as good as flipping a coin. The interpretation of an AUROCC is not very intuitive. Suppose you present the model with two cases. One case has the outcome while the other case has not. The model is blinded to the cases' outcomes. Suppose you ask the model to guess which case has the outcome, and suppose you repeat this process many times. The AUROCC is then equal to the proportion of times that the model will choose the case with the outcome, i.e. choose correctly.

In addition to the AUROCC the calibration of the final model was assessed. A model's

calibration indicates how well predicted outcomes correlate with observed. To assess calibration the predicted probability of early mortality for all patients in the original sample was estimated. The patients were then divided into ten groups, using ten percentiles of the predicted probability of early mortality. In each group, we calculated the proportion with early mortality. Calibration was then assessed visually by plotting observed mortality across the ten groups of predicted mortality. Calibration was also quantified by estimating a calibration slope. A calibration slope of 1 indicates perfect calibration, whereas a calibration slope of < 1 or > 1 indicates that the model overestimates or underestimates the probability of the outcome respectively.

Several sensitivity analyses were done for study II. The primary outcome was early mortality, in hospital, assuming that all patients who were discharged alive before 24 hours were alive at 24 hours. In the first sensitivity analysis a worst-case scenario approach was used to estimate the discrimination of the final model provided this assumption was wrong, and that all patients who were discharged alive before 24 hours were actually dead at 24 hours. In the second sensitivity analysis the final model was compared to a full model that in addition to systolic blood pressure, heart rate, and Glasgow coma scale also included age, sex, transfer status, and mechanism of injury. These additional variables were included in the full model regardless of their statistical significance. Finally, the performance of the final model was compared with that of a reduced model that only included the two strongest predictors.

In study III the model with systolic blood pressure, heart rate, and Glasgow coma scale, as well as the reduced model from study II were validated in a temporally independent sample and compared with established trauma prediction models published by Kondo et al. and Perel et al. (140). The model published by Kondo et al. includes Glasgow coma scale, age, and systolic blood pressure. Perel et al. published one comprehensive model, also available as an online calculator, and a simple model available as a colour chart. Like Kondo's model, Perel's simple model included systolic blood pressure, age, and Glasgow coma scale.

Validation was done by using the final models from study II and the models by Kondo and Perel to estimate the predicted probability of early mortality in this temporally independent sample. The discrimination and calibration of each model were estimated using the same measures as in study II. A bootstrap approach was used to calculate confidence intervals around measures of discrimination and calibration. Exact tests were used to compare discrimination and calibration between models. In addition to discrimination and calibration decision curve analysis was used to estimate the net benefit. This method has been proposed as means to quantify the clinical implications of using a prediction model (173, 174, 182).

The starting point of decision curve analysis is a clinical scenario. For study III a scenario was chosen in which there are several trauma patients in the trauma receiving area that have been surveyed. In monitoring the patients, the clinician may choose to do a repeated survey of everyone, survey no one, or to use a prediction model to decide whom to survey. The net benefit at a specific probability of early mortality, called threshold probability, may be interpreted as the number of patients identified as in need of a repeated survey, without the clinician having to do any unnecessary surveys. This would be a crucial advantage in context where resources are limited.

The goals of study IV were to assess the transferability of a simple prediction model between

different contexts, to assess how updating methods could be used to improve transferability, and to assess the sample size needed to perform updating. Hence, the NTDB dataset described previously was now used in addition to the TITCO dataset used in study II and III. The analysis was conducted stepwise. First, both the TITCO and NTDB datasets were split into three samples, one derivation, one updating, and one validation part. Second, each updating sample was resampled into four samples. While maintaining the proportion of events, Stata's pseudo-random function was used to create subsamples with 10, 25, 50, and 100 events each.

Third, a similar method as the one outlined for study II was used to derive one model in the TITCO derivation data and one model in the NTDB derivation data. Fourth, the TITCO model was then updated in each of the NTDB updating samples and the NTDB model was updated in each of the TITCO updating samples. Two different updating methods were used. The first updating method involved only estimating a calibration intercept that was added to the intercept of the model to be updated. For example, let M_{TITCO} be the model from the TITCO derivation sample (Equation 11):

(11)

$$M_{TITCO} = \beta_{0,TITCO} + \sum_{i=1}^n \beta_{i,TITCO} \omega_{i,TITCO}$$

As noted above, this model was then used to estimate the predicted log odds of early mortality in each of the NTDB updating samples. To estimate the calibration intercept, M_{TITCO} was used as the only independent predictor in a logit regression with early mortality as the dependent variable, and the coefficient of M_{TITCO} , $\beta_{1,CP}$ constrained to 1 (Equation 12).

(12)

$$f_{NTDB}(M_{TITCO}) = \beta_{0,CI} + \beta_{1,CI} M_{TITCO} = \beta_{0,CI} + M_{TITCO}$$

where $\beta_{0,TITCO}$ is the calibration intercept that was added to the original model. Hence, the updated model resulting from the first updating method is defined as (Equation 13):

(13)

$$M_{TITCO}^{U1} = \beta_{0,TITCO} + M_{TITCO}$$

The same process was repeated for the NTDB model in the TITCO updating samples.

The second updating method involved reestimating the coefficients for all parameters included in the original model. Again, using M_{TITCO} as the example, the same parameters as the ones included in M_{TITCO} were created in each of the NTDB updating samples. The coefficients of each parameter, as well as the intercept, were then estimated by including all parameters as independent variables in a logit regression with early mortality as the dependent variable. Each of M_{TITCO} , M_{TITCO}^{U1} , M_{TITCO}^{U2} and were then applied in the NTDB validation sample, and M_{NTDB} , M_{NTDB}^{U1} , M_{NTDB}^{U2} and were applied in the TITCO validation sample. The models were compared in terms of discrimination and calibration, using the same measures as outlined above.

Sample size considerations

The sample size calculations differed between the studies. For study I, already existing datasets were used. Hence, there was no opportunity to influence the number of patients included in each cohort. For study II, ten events per free parameter in the hypothetically most complex model were included. An event was defined as a patient with the outcome, i.e. early mortality. Considering that the candidate predictors were systolic blood pressure, heart rate, and Glasgow coma scale, and assuming that the most complex model would include all these three predictors transformed as restricted cubic splines with four knots and hence be represented by three spline basis functions each, the hypothetically most complex model would have nine free parameters. Applying the ten events per free parameter rule the required number of events were 90, plus all non-events occurring during the same time period.

For study III, published recommendations that prediction model validation studies should include at least 200 events to be adequately powered to detect reductions in predictive performance measures were adhered to (183). Hence, 200 consecutive events and all non-events occurring during the same time period were included. Finally, for study IV, ten events per free parameter in the hypothetically most complex model were used to estimate the sample size required in each derivation sample. As the candidate predictors were the same as in study II, the number of events needed was again 90. A total of 100 events were included in the updating samples, and 100 events in the validation samples.

Missing data

In all four studies multiple imputation using chained equations was used to handle missing data (184). The solution implemented in Stata as `mi impute chained` was employed along with associated `mi` commands. Multiple imputation was used to maximize efficiency under the assumption that data was not missing completely at random but rather missing at random. Patterns of missingness were assessed before deciding on the final imputation model. Continuous variables were imputed using linear regression or predictive mean matching with the ten nearest donors as appropriate. Categorical variables were imputed using simple, ordinal, or multinomial logistic regression as appropriate. Vital signs for which evidence of a non-linear association with early mortality log odds existed were first transformed as restricted cubic splines with five knots placed at equally spaced percentiles before they were imputed using the “just another variable” approach. Auxiliary variables were used in the imputation model. Unless otherwise stated, results are reported using their median and interquartile range across imputed datasets.

Ethical considerations

Trauma research is associated with substantial ethical challenges. According to guidelines published by the Council for International Organizations of Medical Sciences (CIOMS) and WHO there are three general ethical principles that medical research should adhere to (185). The first principle is respect for persons. This principle stipulates that potential research participants should be treated with respect for their autonomy. In trauma research potential participants often have an impaired autonomy and the CIOMS guidelines state that people with impaired autonomy should “be afforded security against harm or abuse”.

This impairment may result from an altered level of consciousness at the time of enrolment. Sometimes potential participants are even unconscious.

All studies in this thesis were granted waivers of informed consent by the relevant ethical bodies. The rationale for applying for waivers of informed consent was that the studies were expected to involve a minimal risk of harm to research participants. In other words, research participants were afforded security against harm and abuse. First, only routine data was collected, i.e. the studies did not include variables that were not expected to be found in patient records. Second, all studies in this thesis were observational. No intervention was assessed. Third, the research was not expected to influence treatment or clinical management.

The second principle is beneficence. This principle is closely related to the first principle as it “refers to the ethical obligation to maximize benefit and to minimize harm”. As alluded to previously there is a considerable lack of observational trauma research from India. In terms of benefit results from such research may inform treatment and clinical management as well as the organization of health systems and policy. Specifically the research in this thesis may contribute to the development of context appropriate decision support tools as well as an increased understanding of predictors of early mortality. Although the risks associated with the research in this thesis are minimal one cannot exclude risks such as an extra person in the resuscitation stealing attention of care providers. However, in this case potential benefits were believed to outweigh potential risks.

The third and final principle is justice, i.e. that the research should benefit the group of people participating in the research. The aim of the research in this thesis was to develop a model for prediction of mortality in urban Indian hospitals. The participants were people presenting to three public university hospitals in urban India. Thus, this research was considered to adhere to the principle of justice, as the research was conducted in a group from the same contexts as the groups that it is later expected to benefit. In addition, the results of this thesis were anticipated to benefit trauma patients globally.

List of ethical bodies and clearances

- I.** LTMGH: Ethics Committee of the Staff and Research Society (amendment to IEC/22/10)
- II.** JPNATC: Institute Ethics Committee All India Institute of Medical Sciences (EC/NP-279/2013 RP-OI/2013). LTMGH: Ethics Committee of the Staff and Research Society (IEC/11/13). SSKM: IPGME&R Research Oversight Committee (IEC/279)
- III.** Same as for study II
- IV.** Same as for study II and III plus clearance for the analysis of NTDB data from the Regional Ethical Review Board in Stockholm (Dnr 2015/426-31)

Personal fieldwork reflections

As alluded to in the preface this project was started while I was still a medical student. In mid 2012 I was halfway through my fourth year at Karolinska Institutet and had two more years

to go. The reason I went to India and Mumbai was to do the surgical component of medical school. Just before I left I had registered as a PhD student, but on a different topic altogether. When I arrived in Mumbai the city was just warming up to the monsoon period. I felt lost, disoriented, and excited all at the same time.

There were several reasons for this state of mind. I travelled alone and entered unknown territory both culturally, clinically, and research wise. I was for example expected to wear a shirt to school and to the hospital where I would be posted. Normally I never wear shirts, but for a while I adapted. Furthermore, my travel to India happened while I was in a vacuum with regards to my research. The Haiti plans had ended abruptly only days before I arrived and I was not sure how to move ahead. However, I was very excited about the prospect of spending an extended period of time in Mumbai. I had high hopes that it would provide a welcome change to the dullness of medical school.

I quickly felt at home in Mumbai and soon stopped feeling disoriented. I primarily divided my time between three places. First and foremost I spent a lot of time at the Roy's residence in Nerul. Nobhojit Roy is the head of the department of surgery at a government hospital in Mumbai, public health researcher, and today fellow PhD-student. He was the one who set up my India trip in the first place. Second, the students' hostel where I was accommodated and third the Lokmanya Tilak Municipal General Hospital where I was posted.

The hospital is located in a central part of Mumbai called Sion and is therefore colloquially known as Sion hospital. It is situated between the two slums Dharavi and Koliwada, just next to a major highway and several local railway lines. Because of its strategic location it has become the main trauma hub of the area. It is a public university hospital and as such has almost every imaginable medical and surgical specialty in-house. Most of its patients come from the neighboring slums. The official number of about 1400 beds does not say much about the actual number of admitted patients as the concept of "floor beds" is well established.

The fact that I soon felt at home did not mean that being an outsider was always easy. My position as both a medical and PhD student caused quite a bit of confusion, both for others and myself. However, as a medical student I quickly gained access to the most intimate parts of the hospital. My presence became well accepted and I was soon more or less free to roam around the hospital area as I wanted. I believe that the speed with which I was granted this privilege was greatly facilitated by my status as a harmless student. Because of differences in education systems between Sweden and India I was a couple of years older than the medical students there. Instead, I was about the same age as the residents and I therefore spent most of my time in hospital with them.

The overall design of this project was developed over the period of five months that I stayed in Mumbai that first time, during countless meetings, dinners, and late evening drives between the hospital and Nerul. I officially changed my PhD topic about halfway through my stay. What would later be known as TITCO was born just before I went back to Sweden. From then on I have been part of the core team working with TITCO. The team has grown recently but in the beginning we were four persons. It was Nobhojit. It was Vineet Kumar, associate professor of surgery at Sion hospital. It was Monty Khajanchi, associate professor of surgery at King Edward Memorial hospital, Mumbai. Finally, it was me. The four of us still run the day-to-day workings of the project. Each week we have project telephone conferences together with the

project officers that perform the data collection.

I went back in early 2013 to assist in starting things up. To recruit centres we visited hospitals in Kolkata, Delhi, Chennai, and Bengaluru. The travelling band consisted of Nobhojit, Johan, my main supervisor, and myself. We met with people who we hoped would be the project focal points and principal investigators at each site. They were often high-ranking surgeons, senior heads of departments. I was always the most junior person in these meetings. Making my voice heard involved playing down the medical student role and focus on my position as an external researcher. Getting surgeons to work together is notoriously difficult but in the end we managed. Later the same year we hosted the first TITCO project meeting in Mumbai and from there we took off. The project officially started when Kolkata received ethical clearance and began data collection in mid 2013.

Since TITCO started I have travelled to India two to three times per year. During these trips I have visited every participating centre and met with principal investigators, local supervisors, and project officers. We discussed data collection issues and I performed quality controls. During the first two years of the project I collated and cleaned the data from all sites and produced weekly to monthly data review reports. Each week the project officer at each site sent me their data and I pulled it together using a combination of different software. I performed error checks and sent potential error back to the project officers for correction.

In general our work has been characterized by a high degree of flexibility and pragmatism. I believe this is a prerequisite for “real-world research” such as this. Things rarely work out exactly as planned but often quite well anyway. Most importantly we have laughed a lot and enjoyed a large number of very good meals together. I think that creating a common sense of achievement and a feeling of us all working together towards the same goal has been key to start the first multi-centre trauma project in India. In the long run, I believe that this project will lead to improved patient outcomes and working conditions of health staff.

main findings and discussion

A young male was the most common trauma patient

The adult trauma patients who presented to three public university hospitals in urban India were about 35 years old [II-IV] (Table 8). A striking majority was male, ranging from 80 to 88% across studies and time periods [I-IV]. Some studies have found being male to be associated with an increased risk of mortality (186), whereas other report males to have better outcomes compared to females (187). In this thesis no evidence that males had an increased risk of mortality compared to females was found (adjusted OR 1.17 95% CI 0.80–1.70, P-value 0.416) [I]. Among all patients the most common mechanisms of injury were road traffic injury and falls [I-IV].

The predominance of males and that road traffic injury and falls were most common corroborate well with previous facility-based research from India (74, 105), and other parts of the world such as Thailand, Germany, and Finland (76, 188). Although these findings cannot be generalised to the population level it is interesting to note the high level of correlation with published population based research from for example Nepal, Sierra Leone, Rwanda, the US, Iran, Vietnam, Pakistan, and Brazil (71-73, 77-81). It seems that young males are over represented in trauma, both on the facility and population level. Potential explanations include different risk profiles of men and women, including use of vehicles, alcohol, and violence.

From a gender perspective a relevant concern is if the male predominance observed in this thesis and in other studies can be explained by a major selection bias. Is it that females to a lower degree reach health facilities after trauma? Unfortunately, the data collected for this thesis cannot be used to answer this question. Interestingly, a study from Sierra Leone found no significant differences in injury mechanisms between males and females in urban areas whereas there was a difference in rural areas. They suggested that this may be because males and females engage in more similar activities in urban areas while activities are to a larger extent governed by traditional gender roles in rural areas (72).

Research from India indicates that females predominate among burn victims. For example, a study based on autopsy reports in the Lucknow Region reported that 87.5% of those who died of burns were females (189). This percentage is the opposite of the percentage of females reported in the studies included in this thesis. However, a subgroup analysis reveals that about 65% of patients with burns that presented to the centres participating in this research were females. A hypothetical explanation is the proximity of major slum areas to participating centres and that it is common with cooking using highly flammable agents in small confined spaces. However, this finding prompts for further research efforts with regards to causes as well as outcomes.

Early mortality remained high by international standards

Between the years 1998 and 2011 early mortality in adult trauma patients was significantly reduced in patients admitted to a public university hospital in Mumbai (adjusted OR 0.56, 95% CI 0.42–0.76, P-value 0.001) [I]. However, it remained high. Overall, early mortality in three public university hospitals in Mumbai, Kolkata, and Delhi was about 8% [II-IV]. As most published studies focus on patients with major trauma it is difficult to find studies to which a valid comparison of mortality figures can be made. For example Hampton et al. found a similar early mortality rate in their study of patients who met the criteria for highest level of

Table 8. Characteristics of study cohorts

	I (n=4189)	II (n=1629)	III (n=2811)*	TITCO		NTDB			
				Derivation (n=1088)	Updating (n=1307)	Validation (n=1333)	Derivation (n=6050)	Updating (n=6745)	Validation (n=5961)
Males (%)	87	80 (78-82)	80 (79-82)	80 (78-82)	81 (79-83)	80 (78-82)	60 (58-61)	59 (58-60)	64 (63-65)
Age**	NA	35 (24-47)	35 (25-46)	34 (24-46)	35 (25-46)	35 (25-46)	52 (31-73)	52 (31-72)	46 (28-65)
Time from injury to arrival	NA	7 (3-28)	7 (3-27)	7 (2-25)	8 (3-30)	7 (2-22)	1 (1-24)	1 (1-2)	1 (1-5)
Transferred (%)	NA	68 (65-70)	71 (69-72)	65 (63-68)	71 (68-73)	71 (68-73)	25 (24-26)	26 (25-27)	24 (23-25)
Mechanism of injury (%)									
Fall	25 (23-26)	27 (25-29)	26 (25-28)	28 (25-30)	26 (24-29)	25 (23-27)	48 (47-49)	47 (45-48)	35 (34-37)
Railway injury	26 (25-27)	7 (6-8)	6 (5-7)	NA	NA	NA	NA	NA	NA
Road traffic injury	36 (35-28)	46 (44-49)	46 (44-47)	NA	NA	NA	NA	NA	NA
Transport injury	[62 (61-64)]***	[53 (51-56)]***	[52 (50-54)]***	53 (50-56)	53 (51-56)	52 (50-55)	32 (31-33)	32 (31-33)	40 (38-41)
Assault	10 (9-11)	9 (7-10)	11 (9-12)	8 (6-10)	9 (7-10)	12 (10-13)	4 (3-4)	4 (4-5)	5 (5-6)
Burn	NA	6 (5-7)	7 (6-8)	6 (5-8)	8 (6-9)	7 (6-8)	2 (2-2)	2 (1-2)	3 (2-3)
Other	1 (1-1)	4 (3-5)	5 (4-5)	5 (3-6)	4 (3-5)	4 (3-5)	14 (14-15)	15 (14-16)	17 (16-18)
Unknown	2 (1-2)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)
Systolic blood pressure	NA	116 (106-125)	120 (110-130)	114 (103-124)	116 (108-128)	120 (110-130)	138 (122-156)	139 (123-156)	137 (122-153)
Heart rate	NA	90 (80-98)	89 (80-98)	88 (80-98)	90 (80-98)	88 (80-98)	86 (74-98)	86 (74-99)	88 (75-100)
Glasgow coma scale	NA	15 (9-15)	15 (9-15)	15 (8-15)	15 (9-15)	15 (9-15)	15 (15-15)	15 (15-15)	15 (15-15)
Early mortality	8	6	7	8 (7-10)	8 (6-9)	8 (6-9)	1 (1-2)	1 (1-2)	2 (1-2)

Table on previous page. Data is presented as median (inter-quartile range) or as proportion (95 % confidence interval). *Does not include the updating sample. **In study I age was not available as continuous variable. Instead age was analysed as a categorical variable. 11% were < 15 years, 82% between 15 and 55 years, and 7% were older than 55 years. ***The sum of railway and road traffic injury. Abbreviations: TITCO Towards Improved Trauma Care Outcomes in India, NA Not applicable, NTDB National Trauma Data Bank

trauma activation in three level one trauma centres in the US (190). Christensen et al. analysed data from eleven countries that participated in a randomised controlled trial of recombinant activated factor VII in bleeding trauma patients (191). They found early mortality rates that ranged from 4 to 13%.

These data indicates that there is scope to improve early mortality outcomes in the context of this thesis. How this is to be achieved remains however a significant knowledge gap. Comparing survivors and non-survivors one finds that the first recorded systolic blood pressure and Glasgow coma scale were considerably lower among non-survivors [II-III]. This finding corresponds well with the global pattern of haemorrhage and traumatic brain injury being main concerns in trauma care (Panel 3 and Figure 5). First, haemorrhage has been estimated to cause the majority of preventable trauma deaths (124). Thus, a closer review of early deaths may reveal abnormalities amendable by intervention such as early blood transfusion and increased focus on damage control resuscitation (130). Second, traumatic brain injury dominates as cause of death in trauma patients (123). In treating traumatic brain injury interventions such as early evacuation of intracranial haematomas are important. However, these deaths are generally considered harder to prevent through clinical intervention. Instead, primary prevention efforts are more likely to be effective in reducing deaths from traumatic brain injury.

Notwithstanding that there are effective clinical interventions that can reduce deaths if implemented, especially from haemorrhage, it is likely that broad based system level interventions are needed. The WHO Guidelines for essential trauma care is one example of a policy document that may guide key decision- and policy makers in strengthening India's trauma system (192). Two recent Lancet commissions highlighted the importance of health and trauma system strengthening to reduce trauma mortality and morbidity (38, 193). These commissions stress the need for coordinated efforts to boost the surgical and anaesthesia workforce, improve blood availability using national blood plans, establish referral and transfer routes, and fund local and national trauma research.

Systolic blood pressure and Glasgow coma scale may be enough to predict early mortality

Early mortality could be accurately predicted using systolic blood pressure, heart rate, and Glasgow coma scale (Table 9) [II-IV]. Restricted cubic splines were used to model the non-linear associations between systolic blood pressure, heart rate, and early mortality (Figure 6) [II]. A model that included systolic blood pressure, heart rate, Glasgow coma scale, age, sex, transfer status, and mechanism of injury did not discriminate significantly better than a model with only systolic blood pressure, heart rate, and Glasgow coma scale (median P-value 0.49) [II]. This finding is interesting considering that trauma research often make a strong case for including at least age and sometimes mechanism in prediction models. For example the

Table 9. Vital sign based models across study II-IV

	II & III		IV (TITCO)	IV (NTDB)
SBP, SBF 1	-0.021 (0.008)	-0.024 (0.006)	-0.027 (0.009)	-0.027 (0.006)
SBP, SBF 2	-0.038 (0.038)	-0.041 (0.036)	-0.038 (0.045)	0.043 (0.041)
SBP, SBF 3	0.339 (0.256)	0.388 (0.244)	0.380 (0.310)	-0.080 (0.170)
HR, SBF 1	-0.003 (0.013)		-0.012 (0.016)	-0.019 (0.011)
HR, SBF 2	-0.016 (0.121)		-0.050 (0.133)	0.144 (0.065)
HR, SBF 3	0.201 (0.559)		0.460 (0.651)	-0.434 (0.208)
GCS	0.205 (0.032)	-0.211 (0.031)	-0.296 (0.043)	-0.280 (0.026)
Intercept	2.214 (0.662)	2.134 (0.577)	4.238 (1.063)	2.789 (0.583)
AUROC	0.846 (0.842-0.850)*	0.846 (0.841-0.849)*	0.919 (0.915-0.920)	0.914 (0.910-0.918)
Calibration slope	1.126 (1.105-1.142)*	1.183 (1.168-1.202)*	0.999 (0.986-1.018)	1.029 (1.027-1.030)

Data is presented as coefficient (standard error) or median (inter-quartile range) across imputed datasets. *Data from study III. Abbreviations: AUROC Area Under the Receiver Operating Characteristics Curve, GCS Glasgow Coma Scale, HR Heart Rate, SBF Spline Basis Function, SBP Systolic Blood Pressure

prediction models published by Kondo, Perel, and Sartorius all include age and the model by Sartorius also includes mechanism (138-140).

Age and mechanism did not add significantly to the discriminatory performance of prediction models in three public university hospitals across urban India [II-III]. There are several hypothetical explanations. First, the age variance in the studied cohort of patients may have been smaller compared to other research. A majority was between 24 and 46 years old with only a small proportion of patients being older than 60 years. It may be that the number

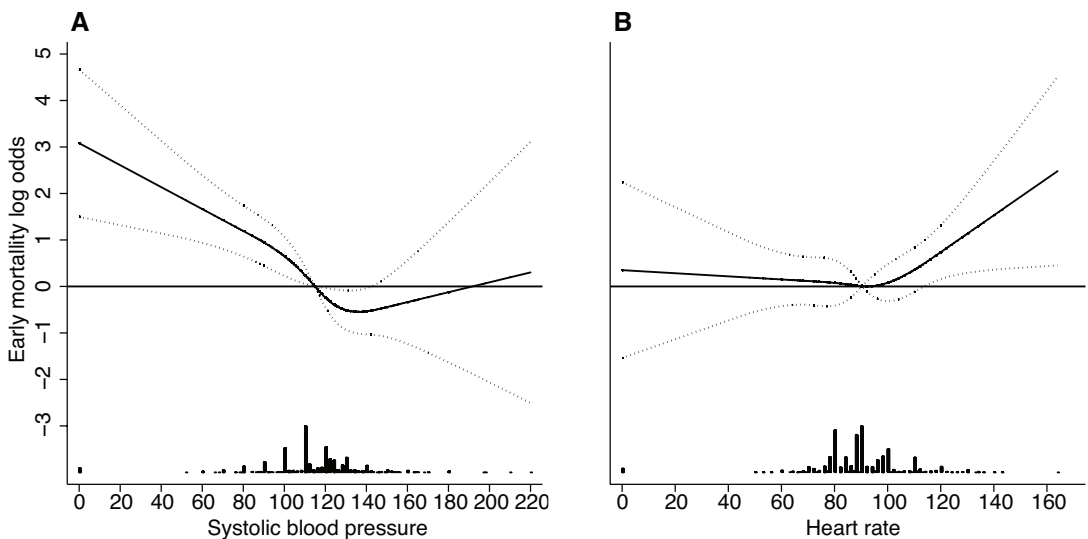


Figure 6A-B. Nonlinear associations between systolic blood pressure, heart rate, and early mortality modelled using restricted cubic splines.

The horizontal solid lines represent log odds=0. The dotplots in the bottom represent density of observed values. A. Adjusted for heart rate and Glasgow coma scale. B. Adjusted for systolic blood pressure and Glasgow coma scale.

of patients with high age was too small to allow for a survival disadvantage to be detected. Second, the outcome was early mortality, i.e. 24-hour mortality. It is possible that the survival disadvantage of older patients observed in other research is more pronounced when late mortality is studied, potentially due to an increased risk of complications.

Furthermore, the model that included only systolic blood pressure and Glasgow coma scale was compared with three other models [III]. The first model was described above and included systolic blood pressure, heart rate, and Glasgow coma scale. The second model was a model published by Kondo (138) and the third model was published by Perel (140). These three models were considered more complex than the model with only systolic blood pressure and Glasgow coma scale. The reason why these models were considered more complex was that to come up with a mortality risk estimate or a final score using any of the three comparison models entailed several more steps compared to using the model with only systolic blood pressure and Glasgow coma scale.

There was no evidence that any of the three more complex models had better discrimination, calibration, or potential clinical implications than the model with only systolic blood pressure and Glasgow coma scale (Figure 7 and 8) [III]. It is worth noting that none of the prediction models for trauma care listed previously include only two variables (Table 6). Instead, most include three or more. The research in this thesis indicates that it is possible to reduce the number of variables in trauma prediction models without losing predictive performance. It is reasonable to assume that a model with only two variables is quicker to apply compared to models that include more variables. Furthermore, a model with only two variables can be presented in a way so that no manual calculations are necessary. Hypothetically, this further increases its feasibility.

There are several reasons why the statement that systolic blood pressure and Glasgow coma scale may be enough to predict early mortality is likely to be regarded as controversial. First, respiratory rate has been found to be a strong predictor of trauma mortality (142, 143). However, trauma research has acknowledged that respiratory rate is often not recorded. This is the case in the three hospitals studied here. Second, heart rate is generally considered one of the earliest signs of circulatory distress whereas a change in blood pressure is considered one of the latest. This is especially true in young people, as their compensatory mechanisms help maintain homeostasis for an extended period of time before they quickly collapse (181). A potential explanation why heart rate did not add significantly to the predictive performance would be that the patients studied here generally arrived to hospital long after the injury [II-III]. In other words, they arrived after long enough for circulation to be affected to the degree that blood pressure has been altered.

The long delay between injury and arrival to participating hospitals can most likely be explained by the fact that 70% of patients were transferred from other hospitals [II-IV]. A valid concern is then if potential treatment administered in the transferring hospital affects the applicability of models based on vital signs in general and systolic blood pressure and Glasgow coma scale in particular. This concern applies equally to the association between prehospital care and model performance. The rationale for this concern would be that the recorded values of vital signs should be interpreted differently depending on if the patient has received treatment or not.

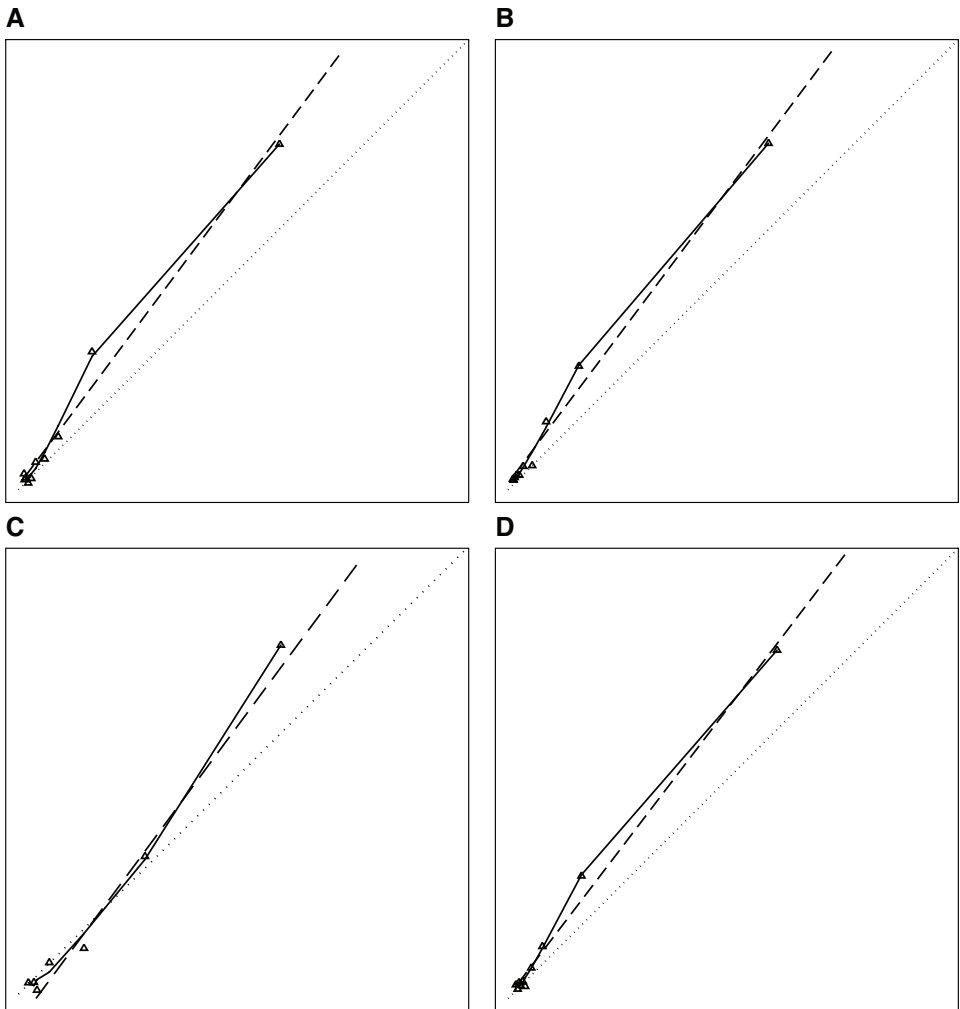


Figure 7A-D. Calibration plots.

On the x-axis is predicted probability of early mortality and on the y-axis is observed probability of early mortality across ten quantiles of predicted early mortality. The dotted line indicates perfect calibration. The solid line indicates a smoothed association between observed and predicted probability of early mortality and the dashed line a graphical representation of the calibration slope. A) Model with systolic blood pressure and Glasgow coma scale B) Model with systolic blood pressure, heart rate, and Glasgow coma scale C) Model by Kondo et al. D) Model by Perel et al.

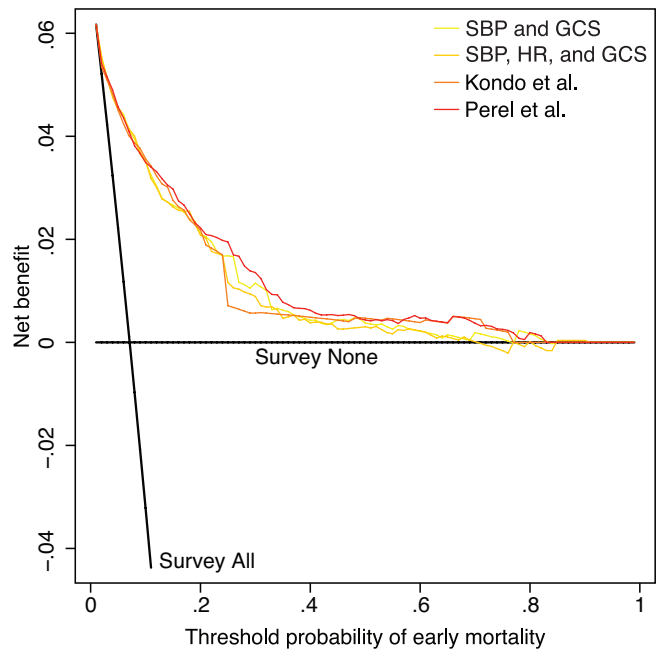
For example, some may argue that a systolic blood pressure of 80 before volume substitution is much less alarming than if it is after adequate transfusion. They are probably right and it is likely that the probability estimates generated by vital signs based prediction models are somewhat conservative in patients that have received vigorous treatment before the model is used. Such conservative estimates are a problem if they may cause patients to be given a lower priority. It is therefore important that the model is used to supplement clinical judgement, not the other way around, particularly in borderline patients.

Calibration was adversely affected by transfer between different contexts but as few as 25 events may be enough to correct this miscalibration

When models that included systolic blood pressure, heart rate,

Figure 8. Decision curves associated with each model.

Kondo's model included Glasgow coma scale, age, and systolic blood pressure, as did Perel's model. In interpreting these curves, one can see that using any of the models tested here is superior to the option of surveying all patients in the range of predicted probabilities of early mortality 0.05-0.2. Using 0.05 as the threshold probability the median net benefit was 0.045 (IQR 0.045-0.046) for the basic model, 0.045 (IQR 0.045-0.045) for the basic model with heart rate, 0.045 (IQR 0.045-0.045) for Kondo's model, and 0.046 (IQR 0.045-0.046) for Perel's model. These figures can be interpreted as using any of these models result in a net of five true positives per 100 patients without increasing the number of false positives, or compared to using no model 45 fewer false positives per 100 patients. In other words, using a model to decide whom to do a repeated survey on instead of surveying everyone would lead to 45 fewer unnecessary surveys per 100 patients. Abbreviations: GCS Glasgow Coma Scale, HR Heart Rate, SBP Systolic Blood Pressure



and Glasgow coma scale were transferred between trauma care contexts in India and the US they still discriminated well. However, calibration was adversely affected in the sense that the TITCO model overestimated the risk of mortality in NTDB patients and the NTDB model underestimated the risk of mortality in TITCO patients (Figure 9 and 10). This miscalibration was easily adjusted using updating methods [IV]. The use of updating methods has been widely propagated in other medical fields than trauma care (168, 194, 195). In the case of a model with seven free parameters 25 events seemed to be enough to achieve acceptable discrimination and calibration in a validation cohort [IV].

In methodologically oriented literature one may find studies that indicate that miscalibration, i.e. under- and overestimation, could be due to difference in outcome prevalence (196). This corroborates well with the results in this thesis, as the model that was trained in data with high outcome prevalence, TITCO, overestimated mortality risk when transferred to a low prevalence context, NTDB. This finding opens for interesting research on the association between outcome prevalence and updating parameters. The first updating method tested involved only the estimation of a calibration intercept that was then added to the original linear prediction. If one found a quantifiable association between the calibration intercept and outcome prevalence this would obviate the need for performing an updating study.

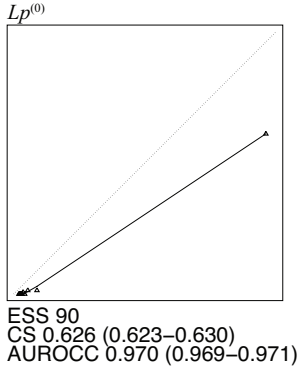


Figure 9. Calibration plots of TITCO models in the NTDB validation sample.

$Lp^{(0)}$ is the unadjusted TITCO model from the TITCO derivation sample. $Lp^{(1,10)}$, $Lp^{(1,100)}$ are after updating by adding a calibration intercept. $Lp^{(2,10)}$, $Lp^{(2,100)}$ are after updating by re-estimating all coefficients. Measures of discrimination and calibration are given as median (inter-quartile range). The effective sample size is expressed in terms of number of events in the sample used to derive or update the models. Triangles represent observed early mortality (y-axis) across ten quantiles of predicted early mortality (x-axis). The dotted line indicates perfect prediction. The solid line indicates a smoothed association between predicted and observed early mortality. Abbreviations: AUROCC Area Under the Receiver Operating Characteristics Curve, CS Calibration Slope, EES Effective Sample Size, NTDB National Trauma Data Bank, TITCO Towards Improved Trauma Care Outcomes.

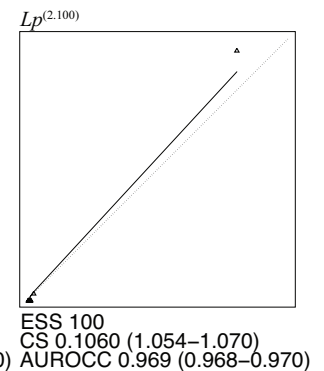
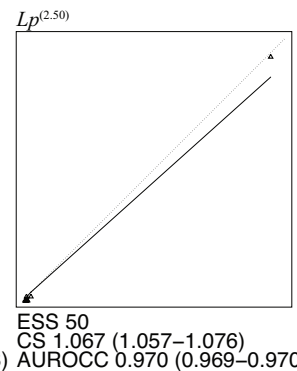
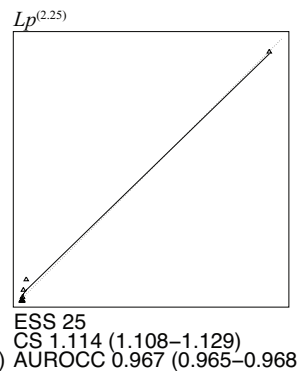
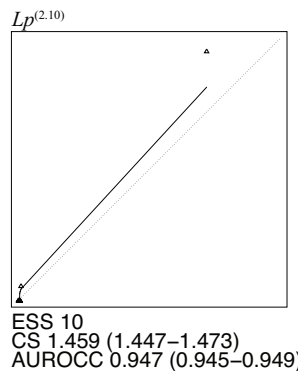
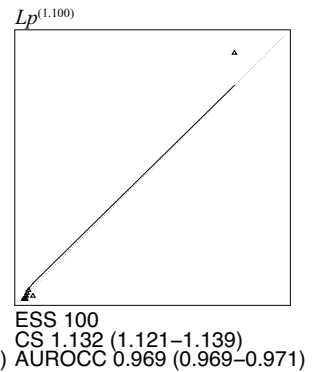
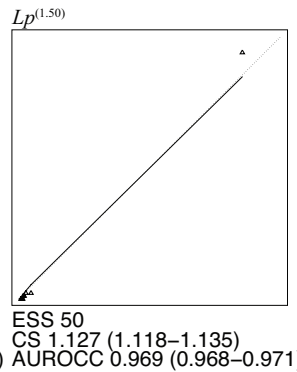
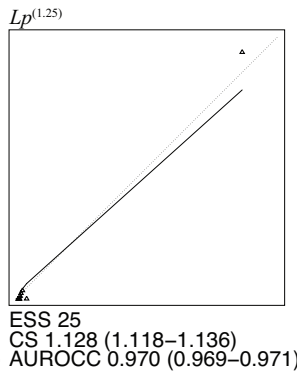
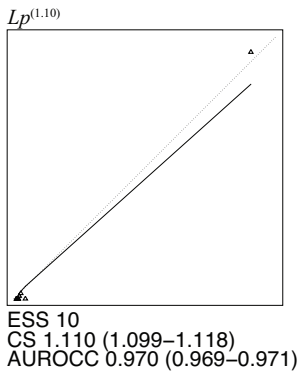
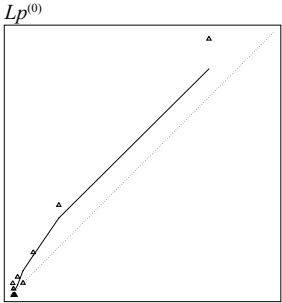
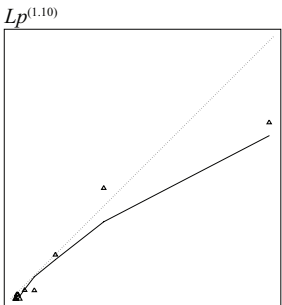


Figure 10. Calibration plots of NTDB models in the TITCO validation sample.

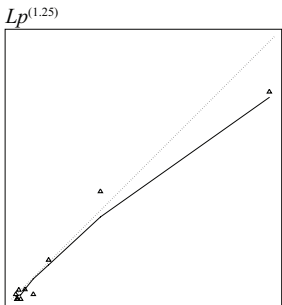
$Lp^{(0)}$ is the unadjusted NTDB model from the NTDB derivation sample. $Lp^{(1,10)}$ - $Lp^{(1,100)}$ are after updating by adding a calibration intercept. $Lp^{(2,10)}$ - $Lp^{(2,100)}$ are after updating by re-estimating all coefficients. Measures of discrimination and calibration are given as median (inter-quartile range). The effective sample size is expressed in terms of number of events in the sample used to derive or update the models. Triangles represent observed early mortality (y-axis) across ten quantiles of predicted early mortality (x-axis). The dotted line indicates perfect prediction. The solid line indicates a smoothed association between predicted and observed early mortality. Abbreviations: AUROCC Area Under the Receiver Operating Characteristics Curve, CS Calibration Slope, EES Effective Sample Size, NTDB National Trauma Data Bank, TITCO Towards Improved Trauma Care Outcomes.



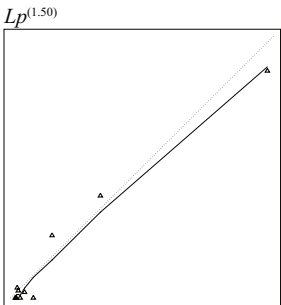
ESS 90
CS 1.553 (1.522–1.589)
AUROCC 0.885 (0.881–0.888)



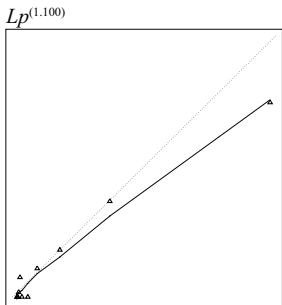
ESS 10
CS 0.889 (0.880–0.904)
AUROCC 0.883 (0.879–0.887)



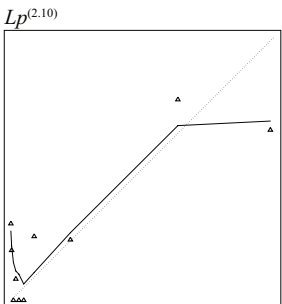
ESS 25
CS 0.957 (0.944–0.966)
AUROCC 0.884 (0.880–0.889)



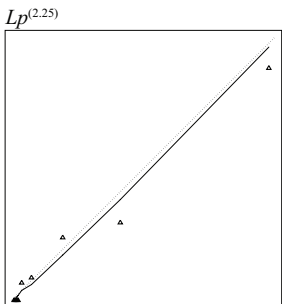
ESS 50
CS 0.955 (0.938–0.975)
AUROCC 0.884 (0.879–0.888)



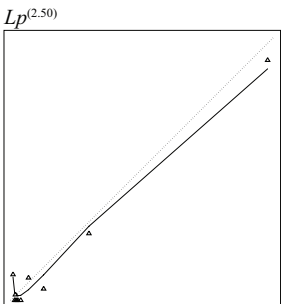
ESS 100
CS 0.922 (0.908–0.938)
AUROCC 0.884 (0.881–0.888)



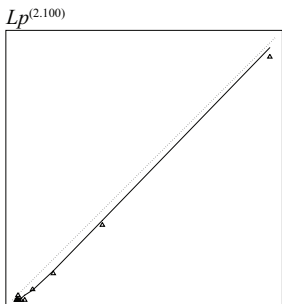
ESS 10
CS 0.783 (0.763–0.804)
AUROCC 0.750 (0.745–0.756)



ESS 25
CS 0.885 (0.871–0.898)
AUROCC 0.880 (0.876–0.884)



ESS 50
CS 0.963 (0.947–0.978)
AUROCC 0.873 (0.868–0.878)



ESS 100
CS 0.954 (0.944–0.971)
AUROCC 0.889 (0.886–0.891)

implications for practice and policy

We will all die. No prediction model in the world can change that, not yet at least. The question is instead when one will die. The research presented here indicates that early mortality in adult trauma patients presenting to three public university hospitals in urban India is not an unpredictable event. It follows on signs that can be measured, parameters that can be recorded. Furthermore this thesis shows that these signs and parameters can be fewer than what conventionally has been suggested. Looking at only two vital signs, systolic blood pressure and Glasgow coma scale, may be enough to predict early mortality.

Mechanical systems thinking in a world of complex adaptive systems

Now, does it make sense to use prediction models, which are conceptually nothing but machines, in the care of trauma patients? After all both the health- and trauma system in which the care is delivered, as well as the patient, are complex adaptive systems. One look at the health systems building blocks and the physiological response to injury, the DAMP, CARS, and MODS of trauma, would probably make many of us to say no, it does not make sense. Much more complex systems are needed.

I would say yes.

- First, the current understanding is that complex adaptive systems can never be predicted in detail. The urge to create complex models for complex systems is really an expression of mechanical systems thinking. Instead, complex adaptive systems often spring from a set of simple rules (1).
- Second, trauma care is highly time dependent. Research indicates that trauma care providers need to make a crucial decision every 72 seconds during the first 30 minutes of initial trauma management (197).
- Therefore, aiding clinical decisions by simplifying complex systems may be particularly important in trauma care.

To elaborate, the ultimate aim of predicting death is to save lives. In this case the connection between death and life is prognosis. The underlying theoretical rationale is straightforward. Clinicians make decisions based on a patient's prognosis. Thus, an accurate estimate of prognosis is important for clinical decision-making. In short, accurate estimates of prognosis lead to better clinical decisions that in turn improve patient outcomes. There is research that shows that clinical prediction models are better at estimating prognosis compared to experienced clinicians, at least in cardiology and intensive care (198, 199). Thus there is reason to believe that prediction models may improve patient outcomes especially.

There is evidence that decision support improves outcomes in trauma care (197). However, in general the literature is divergent when it comes to whether prediction models influence clinical decision making (200, 201). This may partly explain why "prognostic models are abundant in the medical literature yet their use in practice seems limited" (152, 202, 203). However, some prediction models are widely used in clinical practice, for example the Wells score for deep venous thrombosis (204). In trauma care the revised trauma score (RTS) is probably the most used, at least in prehospital trauma triage (143). While few models are used in practice even fewer are ever evaluated for impact (205). This would be the last step needed before a clinical prediction model can be safely introduced in clinical practice, i.e. that it has been showed to

improve outcomes.

Predictions can help guide care and facilitate quality assurance

Now, the main output of this thesis is a prediction model for early mortality in adult trauma patients (Figure 11). Consider the story about Rahul introduced earlier and the flowchart describing a trauma patient's path to hospital (Figure 4). Just as other patients that come directly to the trauma centre in the context of this thesis Rahul followed the dotted line. There was no emergency medical system to call, no ambulance to dispatch. Instead, he was dragged into the police vehicle and driven to Sion hospital. The hospital was never alerted about his imminent arrival.

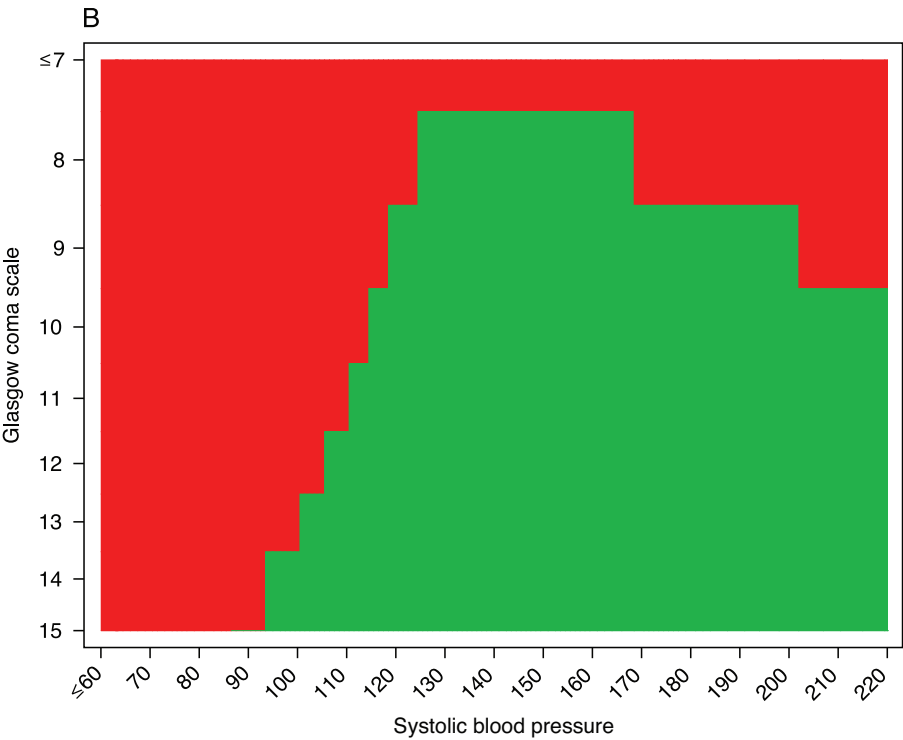
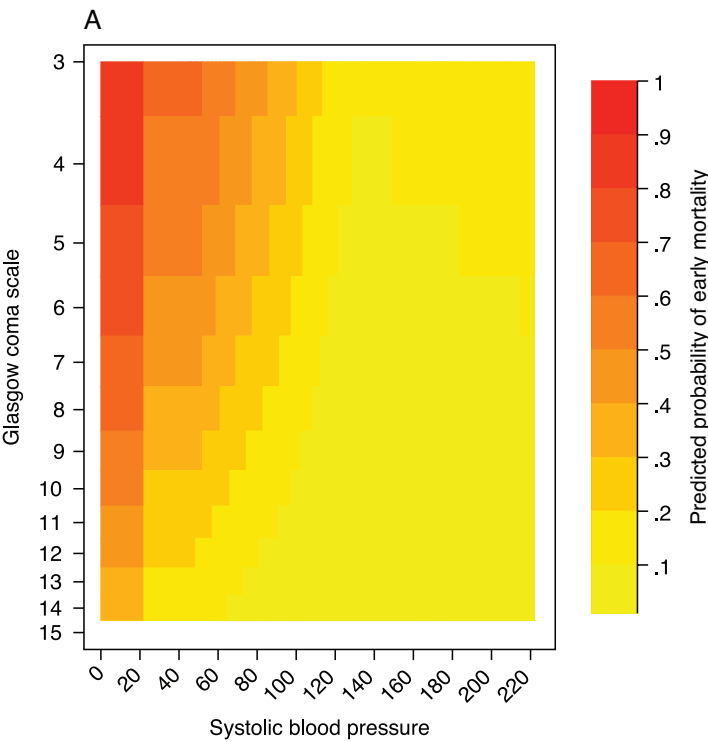
Like many other hospitals in India, Sion hospital only has a rudimentary system for prioritising trauma patients according to need and to identify patients in need of urgent and life-saving interventions. There is no decision support available and although there is a trauma team there are no criteria for different levels of trauma team activation. The most obvious implication for practice derived from this thesis is the potential of incorporating the model based on systolic blood pressure and Glasgow coma scale into a decision support system. Rahul's systolic blood pressure was 110 mmHg and his Glasgow coma scale was 10 on arrival to hospital. Inputting these values into the colour coded chart as part of the assessment of vital signs indicates that he belongs to the red, or severe group (Figure 11B). This output could be associated with a number of simple rules, for example:

- Senior surgical and anesthesia expertise is called to back-up the junior residents on site
- If Rahul is to be taken to the computer tomography (CT) facility he should be accompanied by at least a senior resident, not an intern
- The CT-facility is alerted over phone that Rahul is coming, so that they may cancel any ongoing investigations that are not as urgent
- The operating room is prepared in case Rahul would need surgery
- Rahul should be monitored more closely with new vital signs recordings every 15 minutes to detect any deterioration

Furthermore, the prediction model can help prioritise patients for survey. Consider a scenario where Rahul is not the only person injured in the crash but also the driver and passenger in the taxi that hits him. As a result, there would be four patients rolled into the trauma resuscitation area without warning. The team stationed there would have to split up, but still there would not be enough to cover all four patients. Hence, while the team starts on two patients, the intern or a nurse could use the model to assess the two remaining patients. A patient that is red is then surveyed before a patient that is green.

But what if several patients are red at the same time? One option would be that the intern or nurse goes on to assign a more detailed risk of mortality to each patient and then the patient with the highest risk is surveyed first (Figure 11A). However, it is not obvious that this is the most rationale approach. A patient with a very high risk, for example a patient with a systolic blood pressure that is only barely recordable and a Glasgow coma scale in the range of 3-5 would have an estimated risk of more than 80%, may very well be beyond saving. Instead, a more appropriate approach may be to acknowledge this as outside the limitations of this model

Figure 11A-B. Colour coded charts for obtaining a predicted probability and a triage category based on the model with systolic blood pressure and Glasgow coma scale. B) The cutoff is at a predicted probability of 0.05



and trust senior clinical judgement as such should be available for red patients according to the list above.

Another potential area in which the model can be applied is quality assurance. A straightforward way to use the model for quality assurance would be to use it on all trauma patients presenting to the hospital. One would register the model output, i.e. risk of early mortality, as well as final patient outcome. Then, an interdisciplinary committee of clinicians and decision-makers could for example thoroughly review the green patients who died and discuss these cases on mortality and morbidity meetings in an effort to identify opportunities for improvement. This quality assurance aspect would add the potential of catalyzing system wide change to the model's clinical benefits.

A plan for formal impact evaluation

Before the model can be implemented in clinical practice it needs to undergo a formal impact evaluation (Table 10). The most robust way to perform such an evaluation is a randomized controlled trial. Hospitals would be randomized to either implementing the model or not. However, such a trial would be very costly considering the large number of hospitals needed. The second option would be to randomize clinical units within a smaller number of hospitals. This would be associated with significant risk of spill-over between units using the model and units not using the model. Third, one could consider a temporal cross-over trial, where patients are randomized in blocks time wise. As with the randomization of units, this design is likely to introduce a certain amount of spill-over bias.

The best alternative to a randomized controlled trial in a large number of hospitals is probably an interrupted time series trial (206). In such a trial the baseline mortality would be measured during a specified time period during which no model is available. The model would then be introduced during the course of a couple of months. After this so called roll-out phase the model would then be used in clinical practice for some time. Mortality in the period before the model was introduced would be compared with mortality in the period after the roll-out phase, for example using segmented linear regression.

Table 10. Examples of impact evaluation designs

Design	Unit of analysis	+	-
RCT	Hospital	Robust, best estimate of effect, minimal risk of spill-over bias	Large sample size needed, expensive
RCT	Clinical units	Smaller sample size needed, less expensive	Significant risk of spill-over bias between units in the same hospital
RCT, temporal cross-over	Time (e.g. week, months)	Smaller sample size needed, less expensive	Significant risk of spill-over bias between time periods
Interrupted time series	Time (e.g. week, months)	Robust, small sample size needed, no risk of spill-over bias	Requires substantial amount of time

Abbreviations: RCT Randomized Controlled Trial

A poorly calibrated model may worsen outcomes and waste resources

Another output of this thesis is the finding that prediction models for trauma care may discriminate well but calibrate poorly when they are transferred to a different context. This finding is important both from a clinical and policy perspective. As illustrated above prediction models are used to guide clinical decisions, for example who should be accompanied by a senior resident to the CT or who to survey first. Such decisions are binary and therefore the continuous output, i.e. estimate of probability of early mortality, need to be transformed using a cut-off. This cutoff determines if a patient will be green or red, i.e. accompanied or not accompanied by a senior resident to the CT.

Consider the scenario that a model developed in data from the US is applied in Sion hospital. We know now that this model is highly likely to underestimate the risk of mortality. The cutoff defining red patients will hence be higher compared to if the model had been developed using Sion data. For some patients this difference in cutoff is the difference between being accompanied and not being accompanied, and potentially the difference between life and death. Now, consider the opposite scenario, i.e. a model developed in India is applied in an American trauma centre. This model is likely to overestimate the risk of mortality, and hence suggest that patients who do not really need company to the CT should be accompanied.

Thus, policy makers should be concerned about the validity of prediction models regardless of whether the risk is of under- or overestimation. In the first case they should be concerned with the potential of worsening patient outcomes by introducing a model. In the second case they should be concerned about wasting resources. Clinicians on the other hand are probably more concerned with the risk of losing patients over the risk of wasting resources. Nonetheless, both clinicians and policy makers should want well-calibrated models. This is particularly relevant as an increasing number of practice guidelines include prediction models as tools for risk stratification and to guide treatment decisions, but rarely discuss the validity of these models. For example, the WHO guidelines for essential trauma care reference the trauma score and pre-hospital index for prehospital triage without mentioning when, where, or how these models were derived (192). This needs to change.

One of the missing pieces in India's trauma systems?

The health- and trauma systems in India face severe challenges. A raising trauma burden needs to be tackled as urbanization and motorization are taking place with unprecedented speed. To meet this challenge India needs to strengthen its trauma systems. The question is, which are the missing pieces needed to be found to make this happen (Figure 12)?

- National initiatives are needed to guide and form a trauma agenda, including legislation and safety precautions regarding for example motorization and transportation. With the Supreme Court's judgement the country is on its way but policies like the National Road Safety Policy is needed in other trauma areas as well (63).
- India is one of the countries with the highest volume of trauma and with proper governance it should be possible for India to generate its own trauma evidence. Governance efforts should focus on the science-policy interface, i.e. ensure that research evidence is translated into policy and let policy needs guide research. Furthermore, integrating trauma care

as part of India's efforts to achieve universal health coverage is likely to be pivotal to ensure equity in trauma care (60).

- With regards to service delivery and human researches part of the solution may lie in pushing for a trauma cadre. However existing care providers need to be strengthened first. Currently, surgical residents with a high turnover provide the brunt of trauma care (61). Instead, India should consider focusing on nurses as the focal point for delivering high quality trauma care (207).
- Furthermore, trauma team training and the implementation of guidelines and protocols are needed. If national research is to be boosted then Indian trauma research findings like the results of this thesis need to be fed into national guidelines and protocols.

Prediction models can contribute to several of these processes. They can be integrated into guidelines and protocols as tools for triage, as part of transfer criteria, and for quality assurance. As part of such guidelines and protocols they are used in trauma team training and to improve the understanding of physiology, vital signs, and final outcomes. Keeping prediction models simple increases the feasibility of incorporating them into trauma registries and using them for risk adjustment and comparisons across centres and regions.

Finally, one concrete example of where a prediction model based on systolic blood pressure and Glasgow coma scale may fit in can be found in the operational guidelines for the trauma centre scheme that aims to establish 225 trauma centres along major highways in India (64). These guidelines outline how the trauma centres should be designed, regardless of whether they are built as stand alone trauma centres or incorporated into existing public hospitals. In this design a system for prioritising patients according to need, referred to as triage, is highlighted as fundamental to the care provided within these trauma centres. The model based on systolic blood pressure and Glasgow coma scale should be evaluated as part of this triage process.

Figure 12. Illustration of the “missing pieces” in India’s trauma system and outline of the relevance of prediction models.

Next page

Funding for national
trauma research



Strengthen the trauma
team concept



Establish transfer criteria
and routes



Strengthen existing health
providers in trauma care



National trauma registry



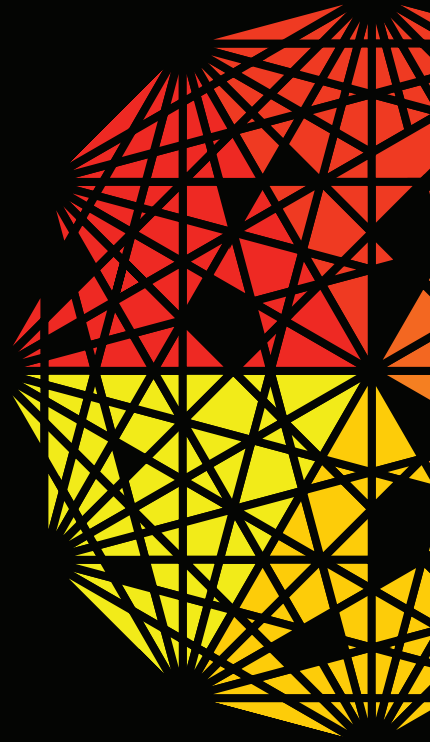
Guidelines and protocols



Boost programs for national fellowships in
trauma care and trauma care as a speciality



Coordination of efforts to
build a national trauma agenda



Trauma care as central to India's efforts to ensure universal health coverage

Trauma team training

Focus on health care providers with low turn-over, such as nurses

Essential trauma care equipment as per WHO guidelines

Focus on the science-policy interface

Service delivery

Financing

Human resources

Medicines and technologies

Governance

Information

Prediction models relevant



methodological considerations

Data quality

All four studies included in this thesis are based on routine data. This means that data has primarily been extracted from patient records. With regards to study I the data were collected before this thesis work was initiated. The 2011 data was collected as part of a WHO multi-centre, multi-country study and there had been a number of control mechanisms employed to ensure the quality of the data. The extent of quality control was less rigorous for the 1998 and 2002 data and it was simply not possible to go back to the original patient records due to local logistic reasons, for example archiving. The rationale for still running the analyses was that this data is likely one of very few datasets being more than 15 years old and hence provided a unique opportunity to study temporal trends.

The TITCO data for study II-IV underwent quality control at two occasions. These control sessions entailed a comparison of the data collected with the data available in patient records. No major deviations were identified. However, no validation of the data available in the patient records was performed. For vital signs data this could have been done by having the project officers also record vital signs, and then comparing the readings of nurses and project officers. There were several reasons why such a validation was not conducted. First, one should be aware that TITCO was politically very sensitive. Combining data from several hospitals allowed for first-time comparisons of for example mortality. When TITCO was initiated it would simply have been very difficult to obtain permission for non-hospital staff to conduct recordings.

Second, trauma is time sensitive and there are a lot of people involved in the initial management of a trauma patient. Double recording of for example vital signs may very well waste valuable time. Hence, the predictions presented in this thesis are predictions based on routine data. As already stated the models need to undergo formal impact evaluation before they can be implemented in clinical practice. Furthermore, it would be interesting to compare these models with models based on well-calibrated live readings, for example conducted by prospective project officers. This should, however, be considered the next step now that analyses of routine data shows promising results.

The routine data limitation applies to NTDB data as well. Individual centres collect data for their own local trauma registries and submit this data to ACS on a yearly basis. Although a large number of error checks are performed on a central level, for example to make sure that no data is outside accepted variable ranges, there is no mechanism for validating the original data. Now, the analyses conducted on NTDB as part of the research in this thesis were mostly concerned with the overall effects of transferring prediction models. It is a methodological question and hence the quality of data is not as important as in for example clinical research, as long as the general data trends can be assumed to be more or less correct.

Missing data

In all studies multiple imputation was used to handle missing data. Multiple imputation is not a new method although it has yet to penetrate properly into the public health and clinical literature. The method provides means to estimate missing values using existing data. The general rationale for using multiple imputation is that one does not need to throw away observations, only because they have missing values in one or more variables. Central to the multiple imputation approach are the concept of missing data patterns and observed versus

non-observed data. Observed data here refers to data that is not missing, i.e. the recorded values of a variable are equal to the “real” values of that variable. Non-observed data refers to the real values of a variable, when the values are missing in the data.

Three missing data patterns are generally discussed, namely that data is missing completely at random (MCAR), at random (MAR), or not at random (MNAR) (184). Data is MCAR when there are no associations between missing data and observed or non-observed data. In other words, missing data in one variable does not depend on the observed or non-observed values of that or any other variable. Data is MAR when there is reason to believe that missing values in one variable can be estimated using non-missing values of other variables. Finally, data is MNAR when the missing values of a variable are dependent on the non-observed values of the same variable. When data is MCAR, which is almost never the case, there is no need to replace the missing data and the results from a complete case analysis will be unbiased. In the cases of MAR or MNAR however, a complete case analysis will be severely biased. In this thesis, data was generally assumed to be MAR.

The prevalence of incomplete observations varied across studies and centres. For example, in study II, the data from the hospital with the maximum proportion of missing data had 51% incomplete observations. This is high. However, it is important to note that this percentage include missing data in so-called auxiliary variables. These are variables that are included in the imputation model to maximize the performance of the multiple imputation algorithm, i.e. to provide estimates of the variables of interest that are as close to their “real”, unobserved, values as possible. The imputation model for study II included 15 variables. All it takes for an observation to be classified as incomplete is that it has a missing value in any of these 15 variables.

Analysis method

“Shit in, shit out” is a common expression encountered in discussions on data analysis. It refers to the fact that findings are only as good as the original data, and that no analysis techniques, no matter how advanced, can change that. The analysis methods employed in this thesis may appear to some as rather advanced. However, if one breaks it down what materialises is the simple logistic regression, one of the most common analysis methods in all of public health and clinical medicine research. Now, many would actually argue that a logistic regression is not advanced enough for the task at hand, i.e. to develop a prediction model. Other methods are available and are gaining in popularity, such as Random forests and Bayesian belief networks. These methods can be regarded as considerably more advanced but there is little evidence that they improve predictions over simple logistic regression (183, 208).

The models presented in this thesis were never tested in each hospital separately. This is a limitation because as highlighted earlier the three Indian hospitals that study II-IV are based on differ quite substantially (Figure 3). Whereas LTMGH and SSKM are general hospitals JPNATC is a stand along trauma centre. It is likely that not only structures but also outcomes differ between these hospitals. Therefore referring to them as one context may be somewhat of a misrepresentation. Drawing on the results of study IV one can expect that the model based on systolic blood pressure and Glasgow coma scale will underestimate the risk of early mortality in centres with a mortality rate that exceeds that of the aggregate data. Similarly the model

may overestimate the risk of early mortality in centres with a mortality rate that is lower than that of the aggregate data. Before implementation and impact evaluation separate validation studies including updating methods should be conducted.

Eligibility criteria

In general the inclusion criteria employed in this thesis were very broad. It is common in trauma research to use some injury severity score as part of the inclusion criteria. One of the most commonly employed scores is the injury severity score (ISS) (209). The score ranges from 0 to 75 where 0 indicates no injury and 75 the most severe injury possible. For example, a common inclusion criterion in studies of major trauma is $ISS > 15$. The reason why ISS or similar scores have not been used as an inclusion criterion in this thesis is that ISS, like all anatomical injury severity scores, is a retrospective score. It cannot be calculated until a patient has undergone all examinations considered reasonable to identify any injury that may contribute significantly to ISS.

In other words, consider the scenario in which an unconscious and circulatory unstable trauma patient arrives to hospital after a road traffic crash. To get a fair idea of this patient's ISS he or she would at least need to undergo a CT-scan. However, in the context of this thesis, such a patient may not survive long enough to reach the CT-scan or any other imaging. As a result, the final ISS may turn out very low, say three, even though the "real" ISS may be as high as 75 due to a combination of injuries to the head, thorax, and abdomen. In other words, it is unlikely that ISS, or most other anatomical injury severity scores, provides a fair representation of the actual severity of the patients in the context of this thesis.

Furthermore, all inclusion criteria that are assigned retrospectively, such as significant haemorrhage, traumatic brain injury, etcetera, defeats the purpose of a prediction model that is supposed to be applied prospectively. This thesis aims to develop a prediction model that can be applied to any trauma patient, be it a patient that is transferred from another hospital with the actual incident occurring more than 24 hours earlier or a patient that arrives right from the railway track, at the point of arrival to the hospitals participating in the studies. This approach is very pragmatic and is likely to result in a loss of predictive performance compared to a model developed for a much less heterogenic patient sample.

Generalisability

The validation of models in study III shows that the predictions based on study II can be generalised to a temporally independent sample. Hence, they are generalisable temporally. Furthermore, systolic blood pressure, heart rate, and Glasgow coma scale were predictive in both the TITCO and NTDB samples. Thus, the combination of these three vital signs as predictive of trauma mortality was generalisable, even though the exact models needed some adjustment to fit a new context. Finally, the challenges faced by the public university hospitals that participated in TITCO, including high volumes and transfer rates, are likely to be shared by other public university hospitals across urban India and in other countries with similar demography.

Both the TITCO and NTDB samples can rightly be described as facility based convenience samples. First, the fact that they are facility based disqualifies any attempts to extrapolate the

results to the general population. Hence, no such attempts have been made. Second, neither TITCO nor NTDB can be claimed to be representative of the trauma patient population in their respective country of origin. TITCO even less than NTDB, as India has such a wide variety of public and private providers that all to some extent are involved in trauma care. Therefore, no claims are made that the models presented in this thesis will work in other hospitals than the ones that participated.

Outcome

Early mortality was the outcome in all four studies. As alluded to previously, the rationale for using this outcome was that the probability of early mortality indicates an urgent need for intervention. The focus on early mortality does not mean that later mortality is less important, but the probability of for example death in hospital within 30 days is arguable more difficult to interpret clinically, at least in early management. Furthermore, there are many other outcomes that are as important as mortality. Quality of life and other functional outcomes are of course crucial also in trauma research, especially as mortality rates improve.

An ethical dilemma that arises in trauma research, care, and quality improvement schemes is the fact that people may regard some outcomes as worse than death. As stated previously the aim of predicting death is to save lives, but what if life is being bound to a ventilator? Or having no motor or sensory function below nipple level? These questions are particularly relevant in contexts with very limited resources, as caring for such patients is associated with high costs for society, and even more often for the family and relatives of the patient. Therefore, it is vital that trauma research aiming to identify interventions that can save lives is accompanied by careful evaluation of the effect on quality of life among survivors.

conclusions and recommendations

- **Between** 1998 and 2011 early mortality declined among patients with major trauma in a public university hospital in Mumbai despite the absence of a trauma system and functioning prehospital organisation [I]
- **Between** October 2013 and July 2014 early mortality was about 8% in adult trauma patients presenting to three public university hospitals in urban India [II-IV]
- **Comparatively** more complex models did not outperform a model based only on systolic blood pressure and Glasgow coma scale in predicting early mortality [II-III]
- **When** vital sign based prediction models for early mortality in adult trauma patients were transferred between an Indian and an US context the Indian model overestimated the risk of early in US patients and the US model underestimated the risk in Indian patients [IV]
- **This** miscalibration could be adjusted using statistical updating methods in samples with as few as 25 events [IV]

First, early mortality in three public university hospitals in urban India remained high by international standards. As expected substantial differences in systolic blood pressure and Glasgow coma scale were observed between non-survivors and survivors. This finding is in line with international patterns and indicates that haemorrhage and traumatic brain injury are major clinical issues.

Second, sooner or later Indian hospitals will implement systems to prioritise trauma patients according to need and to identify patients in need of urgent and life-saving interventions. Indian clinicians and decision- and policy makers should then consider evaluating decision support that include vital signs, like the model based on systolic blood pressure and Glasgow coma scale presented in this thesis.

Third, when treatment guidelines and protocols for trauma care include prediction models they need to transparently report when, where, and how these models were developed. They also need to clearly cite the original derivation study as well as potential subsequent validation studies. This is needed to enable trauma care providers and policy-makers to assess whether a specific model is appropriate for their context.

Fourth, validation studies of logistic prediction studies should explicitly include an updating component. If a calibration intercept is estimated, or a reestimation of coefficients of a model with seven or less free parameters this component should entail the enrolment of at least 25 patients with the outcome in addition to the traditionally suggested 100 patients needed for external validation.

To synthesise, early mortality in adult trauma patients admitted to three public university hospitals in urban India could be predicted. However, caution is crucial when transferring vital signs based models between different contexts, such as between low, middle, and high resource trauma contexts. Both over- and underestimation of mortality can occur if a model is applied out of its correct context. The findings are relevant from both a clinician and a health systems perspective in order to estimate the risk of dying for trauma victims.

“

The only useful function of a statistician is to make predictions”

- W. Edwards Deming

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Johan

I was your first PhD student. I learnt a lot. For the benefit of future students I would like to share a step-by-step guide on how to revise a paper with you as supervisor. Let r_0 denote the first draft. Let r_1 denote the first revision, r_2 the second revision, and so on if needed. Then:

1. Send r_0 to Johan
2. Wait for the email saying “GOOD START! Comments attached. Johan”
3. Quickly click the “accept all changes” button, this way, the fact that EVERYTHING has been marked red can be quickly forgotten*
4. Change the title according to the suggestion that follows the comment “BORING!! Is this the best you can do?” **,
5. Change the aim according to the suggestion that follows the comment “Is this an aim?” **,
6. Send r_1 to Johan
7. Repeat step 2-5
8. Send r_2 to Johan
9. See step 2 above
10. Wait for two days more
11. Repeat step 1
12. Wait for the email saying “Good job!”
13. Submit r_0 to target journal

Johan, when people ask me why I work with you I usually answer them that it's not always easy. Then I tell them that I've never met someone who's so flexible. Who gives me so much space to be myself. Who opens so many doors. We both know that without you I wouldn't have reached here. Thank you.

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Way back you sent me this quote:

“Ortopeder är lite snyggare, lite smartare, lite större och framförallt tjänar de mycket mer pengar” – Okänd

Let me try to translate into English: Orthopaedic surgeons look better, are smarter, bigger and most importantly, they earn a lot more money.

Says it all, doesn't it?

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*If you feel like crying quickly scroll down to the methods section of your paper and you'll notice that there are much fewer comments here. Take a deep breath before you scroll up again. **If there is no suggestion (quite often the case) just shuffle the words in a random manner. Take a deep breath.

Anneli, Emma, Kim, Lina

Now that this guerrilla PhD is over I'll do what I can to help you fight your battles, just as you've helped me fight mine.

India

The India I know is all beginnings. It's hot, wet, suffocating. My India is like its rain. It doesn't obey the laws of physics. Instead, it's a merciless assault coming from all directions at once, making an umbrella look like the most useless invention ever. My India opens the door and tells you that you've been missed. Even if it's all your fault because you've lost your phone. It's food. And people. And food with people who thinks sharing is the only way to have food. Who believes sharing is how the world works.

Nobhojit

My partner in crime. When we're done the world won't be the same.

Anita

My Indian mum. For telling me that I look thin and have to eat. For taking me out to have proper food in nice, clean, places (not dumps like Nobhojit).

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Sticky cake ftw!!

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Sid

You talk too much. But because you always give me soan papdi I forgive you.

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Jyoti, Mangesh, Debojit, Santosh, Dusu, Veera

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